

A201398K1B

by BL

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 September 2002 (19.09.2002)

PCT

(10) International Publication Number
WO 02/072570 A2

(51) International Patent Classification⁷: C07D 401/00

(US). LI, Ge; Building 7, Room 201, LuJiaZui Garden,
LuJiaZui, Shanghai (CN).

(21) International Application Number: PCT/US02/07106

(74) Agent: JEANETTE, Henry, C.; Schering-Plough Corporation, Patent Department - K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(22) International Filing Date: 11 March 2002 (11.03.2002)

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VN, YU, ZA, ZM.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/275,417 13 March 2001 (13.03.2001) US

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).



(71) Applicants: SCHERING CORPORATION [US/US]; Patent Department - K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). PHARMA-COPEIA, INC. [US/US]; 3000 Eastpark Boulevard, Cranbury, NJ 08512 (US).

(72) Inventors: ROSENBLUM, Stuart, B.; 16 Steven Terrace, West Orange, NJ 07052 (US). ZENG, Qingbei; 509 Cinder Road, Edison, NJ 08820 (US). MUTAHI, Mwangi, Wa; 45 Snyder Road, Fords, NJ 08863 (US). ASLANIAN, Robert, G.; 144 Philip Drive, Rockaway, NJ 07866 (US). TING, Pauline, C.; 74 Delwick Lane, New Providence, NJ 07974 (US). SHIH, Neng-Yang; 1 Maple Drive, North Caldwell, NJ 07006 (US). SOLOMON, Daniel, M.; 9 Marshall Drive, Edison, NJ 08817 (US). CAO, Jianhua; 203 Country Club Lane, Scotch Plains, NJ 07076 (US). VACCARO, Henry, A.; 123 Somerset Avenue, South Plainfield, NJ 07080 (US). MC CORMICK, Kevin, D.; 5 Pace Drive, Edison, NJ 08820 (US). BALDWIN, John, J.; 621 Gypsy Hill Circle, Gwynedd Valley, PA 19437

Declaration under Rule 4.17:

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

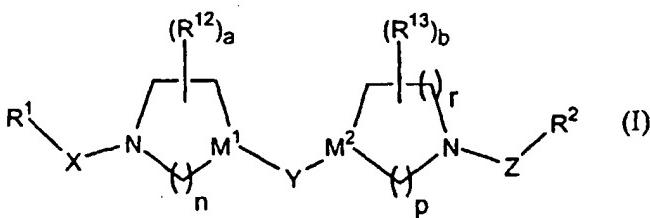
Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A2

(54) Title: NOVEL NON-IMIDAZOLE COMPOUNDS



(57) Abstract: Disclosed are novel compounds of the formula (I). Also disclosed are pharmaceutical compositions comprising the compounds of Formula (I). Also disclosed are methods of treating various diseases or conditions, such as, for example, allergy, allergy-induced airway responses, and congestion (e.g., nasal congestion) using the compounds of Formula (I). Also disclosed are

methods of treating various diseases or conditions, such as, for example, allergy, allergy-induced airway responses, and congestion (e.g., nasal congestion) using the compounds of Formula (I) in combination with a H1 receptor antagonist.

NOVEL NON-IMIDAZOLE COMPOUNDS

BACKGROUND OF THE INVENTION

WO 95/14007 published May 26, 1995 discloses H₃ receptor antagonists of the imidazole type.

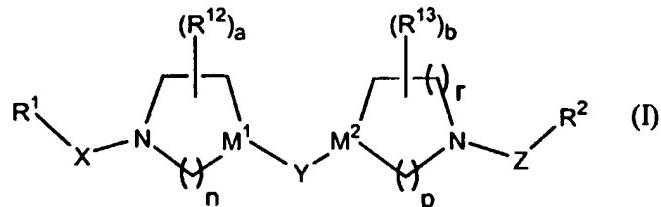
WO99/24405 published May 20, 1999 discloses H₃ receptor ligands of the imidazole type.

US 5,869,479 issued February 9, 1999 discloses compositions for the treatment of the symptoms of allergic rhinitis using a combination of at least one histamine H₁ receptor antagonist and at least one histamine H₃ receptor antagonist.

In view of the art's interest in compounds which affect H₃ receptors, novel compounds that are antagonists of H₃ receptors would be a welcome contribution to the art. This invention provides just such a contribution.

Summary of the Invention

The present invention provides novel compounds of structure I.



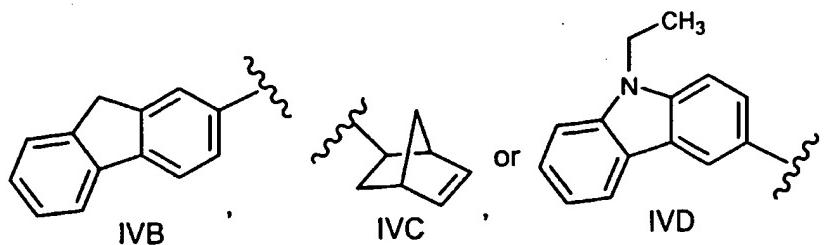
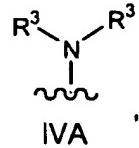
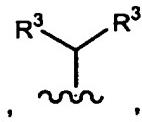
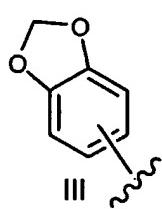
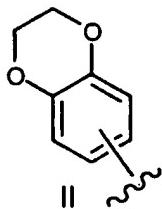
or a pharmaceutically acceptable salt or solvate thereof, wherein:

(A) R¹ is selected from:

- (1) aryl;
- (2) heteroaryl;
- (3) heterocycloalkyl
- (4) alkyl;

- 2 -

- (5) $-\text{C}(\text{O})\text{N}(\text{R}^{4\text{B}})_2$;
- (6) cycloalkyl;
- (7) arylalkyl;
- (8) heteroaryl/heteroaryl (e.g., isoxazoylthienyl or pyridylthienyl); or
- (9) a group selected from:



said aryl (see (A)(1) above), heteroaryl (see (A)(2) above), aryl portion of arylalkyl (see (A)(7) above), phenyl ring of formula II (see (A)(9) above), phenyl ring of formula III (see (A)(9) above), phenyl rings of formula IVB (see (A)(9) above), or phenyl rings of formula IVD (see (A)(9) above) are optionally substituted with 1 to 3 substituents independently selected from:

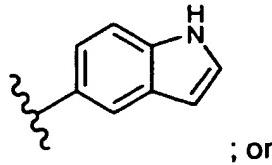
- (1) halogen (e.g., Br, F, or Cl, preferably F or Cl);
- (2) hydroxyl (i.e., -OH);
- (3) lower alkoxy (e.g., C₁ to C₆ alkoxy, preferably C₁ to C₄ alkoxy, more preferably C₁ to C₂ alkoxy, most preferably methoxy);
- (4) -Oaryl (i.e., aryloxy);
- (5) -SR²²;
- (6) -CF₃;
- (7) -OCF₃;
- (8) -OCHF₂;
- (9) -NR⁴R⁵;

- 3 -

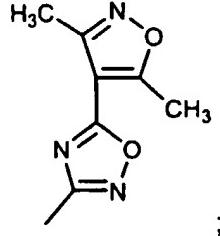
- (10) phenyl;
- (11) NO_2 ,
- (12) $-\text{CO}_2\text{R}^4$;
- (13) $-\text{CON}(\text{R}^4)_2$ wherein each R^4 is the same or different;
- (14) $-\text{S}(\text{O})_2\text{R}^{22}$;
- (15) $-\text{S}(\text{O})_2\text{N}(\text{R}^{20})_2$ wherein each R^{20} is the same or different;
- (16) $-\text{N}(\text{R}^{24})\text{S}(\text{O})_2\text{R}^{22}$;
- (17) $-\text{CN}$;
- (18) $-\text{CH}_2\text{OH}$;
- (19) $-\text{OCH}_2\text{CH}_2\text{OR}^{22}$;
- (20) alkyl (e.g., C_1 to C_4 , such as methyl);
- (21) substituted phenyl wherein said phenyl has 1 to 3 substituents independently selected from alkyl, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OCHF}_2$, -Oalkyl;
- (22) -Oalkylaryl (preferably -Oalkylphenyl or -Oalkyl-substituted phenyl, e.g., $-\text{OCH}_2$ dichlorophenyl, such as $-\text{OCH}_2$ -2,6-dichlorophenyl or $-\text{OCH}_2$ -2-chloro-6-fluorophenyl) wherein said aryl group is optionally substituted with 1 to 3 independently selected halogens; or
- (23) phenyl;
- (B) X is selected from alkyl (e.g., $-(\text{CH}_2)_q$ - or branched alkyl) or $-\text{S}(\text{O})_2$ -;
- (C) Y represents
 - (1) a single bond (i.e., Y represents a direct bond from M^1 to M^2); or
 - (2) Y is selected from $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, $-(\text{CH}_2)_q-$, or $-\text{NR}^4\text{C}(\text{O})-$; with the provisos that:
 - (a) when M^1 is N, then Y is not $-\text{NR}^4\text{C}(\text{O})-$; and
 - (b) when Y is a bond, then M^1 and M^2 are both carbon;
- (D) M^1 and M^2 are independently selected from C or N;
- (E) Z is selected from: $\text{C}_1\text{-C}_6$ alkyl, $-\text{SO}_2$ -, $-\text{C}(\text{O})-$ or $-\text{C}(\text{O})\text{NR}^4-$;
- (F) R^2 is selected from:
 - (1) a six-membered heteroaryl ring having 1 or 2 heteroatoms independently selected from N or N-O (i.e., N-oxide), with the remaining ring atoms being carbon;

- 4 -

- (2) a five-membered heteroaryl ring having 1 to 3 heteroatoms selected from nitrogen, oxygen, or sulfur with the remaining ring atoms being carbon; or
- (3) an alkyl group, preferably a C₁ to C₄ alkyl group, more preferably methyl;
- (4) an aryl group, e.g., phenyl or substituted phenyl (preferably phenyl), wherein said substituted phenyl is substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, -OCF₃, -CF₃, -CN, -NO₂, -NHC(O)CH₃, or -O(CH₂)_qN(R^{10A})₂;
- (5) -N(R^{11A})₂ wherein each R^{11A} is independently selected from: H, alkyl (e.g., i-propyl) or aryl (e.g., phenyl), preferably one R^{11A} is H and the other is phenyl or alkyl (e.g., i-propyl);
- (6) a group of the formula:



- (7) a heteroarylheteroaryl group, e.g.,



said five membered heteroaryl ring ((F)(2) above) or six-membered heteroaryl ring ((F)(1) above) is optionally substituted with 1 to 3 substituents selected from:

- (a) halogen;
- (b) hydroxyl;
- (c) lower alkyl;
- (d) lower alkoxy;
- (e) -CF₃;
- (f) -NR⁴R⁵;
- (g) phenyl;
- (h) -NO₂;
- (i) -C(O)N(R⁴)₂ (wherein each R⁴ is the same or different);

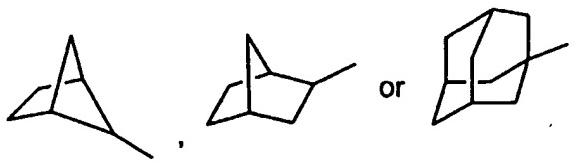
- 5 -

- (j) $-\text{C}(\text{O})_2\text{R}^4$; or
- (k) phenyl substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, $-\text{OCF}_3$, $-\text{CF}_3$, -CN, $-\text{NO}_2$ or $-\text{O}(\text{CH}_2)_q\text{N}(\text{R}^{10A})_2$;
- (G) R^3 is selected from:
 - (1) aryl;
 - (2) heteroaryl;
 - (3) heterocycloalkyl
 - (4) alkyl; or
 - (5) cycloalkyl;
 wherein said aryl or heteroaryl R^3 groups is optionally substituted with 1 to 3 substituents independently selected from:
 - (a) halogen (e.g., Br, F, or Cl, preferably F or Cl);
 - (b) hydroxyl (i.e., $-\text{OH}$);
 - (c) lower alkoxy (e.g., C_1 to C_6 alkoxy, preferably C_1 to C_4 alkoxy, more preferably C_1 to C_2 alkoxy, most preferably methoxy);
 - (d) $-\text{Oaryl}$ (i.e., aryloxy);
 - (e) $-\text{SR}^{22}$;
 - (f) $-\text{CF}_3$;
 - (g) $-\text{OCF}_3$;
 - (h) $-\text{OCHF}_2$;
 - (i) $-\text{NR}^4\text{R}^5$;
 - (j) phenyl;
 - (k) $-\text{NO}_2$,
 - (l) $-\text{CO}_2\text{R}^4$;
 - (m) $-\text{CON}(\text{R}^4)_2$ wherein each R^4 is the same or different;
 - (n) $-\text{S}(\text{O})_2\text{R}^{22}$;
 - (o) $-\text{S}(\text{O})_2\text{N}(\text{R}^{20})_2$ wherein each R^{20} is the same or different;
 - (p) $-\text{N}(\text{R}^{24})\text{S}(\text{O})_2\text{R}^{22}$;
 - (q) -CN;
 - (r) $-\text{CH}_2\text{OH}$;
 - (s) $-\text{OCH}_2\text{CH}_2\text{OR}^{22}$; or
 - (t) alkyl;

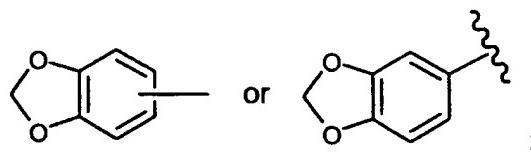
- 6 -

(H) R^4 is selected from:

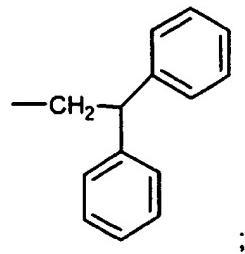
- (1) hydrogen;
- (2) C₁-C₆ alkyl;
- (3) cycloalkyl;
- (4) cycloalkylalkyl (e.g., cyclopropyl-CH₂- or cyclohexyl-CH₂-);
- (5) heterocycloalkylalkyl (e.g., tetrahydrofuryl-CH₂-);
- (6) bridged bicyclic cycloalkyl ring, such as, for example:



- (7) aryl having a fused heterocycloalkyl ring bound to said aryl ring, preferably the heteroatoms in said heterocycloalkyl ring are two oxygen atoms, e.g., phenyl having a heterocycloalkyl ring bound to said phenyl ring, such as

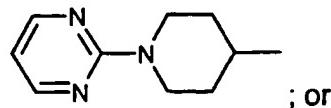


- (8) aryl;
- (9) arylalkyl;
- (10) alkylaryl;
- (11) -(CH₂)_dCH(R^{12A})₂ wherein d is 1 to 3 (preferably 1), and each R^{12A} is independently selected from phenyl or substituted phenyl, said substituted phenyl being substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, -OCF₃, -CF₃, -CN, or -NO₂, e.g.,



- (12) heterocycloalkylheteroaryl, e.g.,

- 7 -



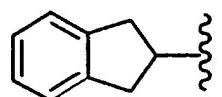
; or

(13) -(C₁ to C₆)alkylene-O-R²² (e.g., -C₃H₆OCH₃);

wherein the aryl R⁴ group, the aryl portion of the arylalkyl R⁴ group, or the aryl portion of the alkylaryl R⁴ group is optionally substituted with 1 to 3 substituents independently selected from:

- (a) halogen;
- (b) hydroxyl;
- (c) lower alkyl;
- (d) lower alkoxy;
- (e) -CF₃;
- (f) -N(R²⁰)(R²⁴),
- (g) phenyl;
- (h) -NO₂;
- (i) -C(O)N(R²⁰)₂ (wherein each R²⁰ is the same or different),
- (j) -C(O)R²²;
- (l) -(CH₂)_k-cycloalkyl;
- (m) -(CH₂)_q-aryl; or
- (n) -(CH₂)_m-OR²²;

(I) each R^{4B} is independently selected from: H, heteroaryl (e.g., pyridyl), alkyl, alkenyl (e.g., allyl), a group of the formula



arylalkyl (e.g., benzyl), or arylalkyl wherein the aryl moiety is substituted with 1-3 substituents independently selected from: halogen (e.g. -CH₂-p-Clphenyl); preferably one R^{4B} is H;

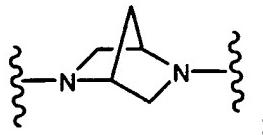
(J) R⁵ is selected from: hydrogen, C₁-C₆ alkyl, -C(O)R²⁰ (e.g., -C(O)alkyl, such as -C(O)CH₃, -C(O)₂R²⁰, -C(O)N(R²⁰)₂ (wherein each R²⁰ is the same or different));

(K) each R^{10A} is independently selected from H or C₁ to C₆ alkyl (e.g., methyl), or each R^{10A}, taken together with the nitrogen atom to which they are bound, forms a 4 to 7 membered heterocycloalkyl ring;

- 8 -

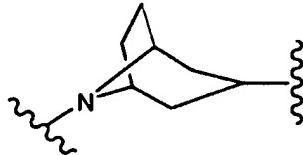
(L) R¹² is

- (1) selected from alkyl, hydroxyl, alkoxy, or fluoro, provided that when R¹² is hydroxy or fluoro then R¹² is not bound to a carbon adjacent to a nitrogen; or
- (2) R¹² forms an alkyl bridge from one ring carbon to another ring carbon, an example of such a bridged ring system is:



(M) R¹³ is

- (1) selected from alkyl, hydroxyl, alkoxy, or fluoro, provided that when R¹³ is hydroxy or fluoro then R¹³ is not bound to a carbon adjacent to a nitrogen; or
- (2) R¹³ forms an alkyl bridge from one ring carbon to another ring carbon, an example of such a bridged ring system is:



(N) R²⁰ is selected from hydrogen, alkyl, or aryl, wherein said aryl group is optionally substituted with from 1 to 3 groups independently selected from: halogen, -CF₃, -OCF₃, hydroxyl, or methoxy; or when two R²⁰ groups are present, said two R²⁰ groups taken together with the nitrogen to which they are bound form a five or six membered heterocyclic ring;

(O) R²² is selected from: heterocycloalkyl (e.g., morpholinyl or pyrrolidinyl), alkyl or aryl, wherein said aryl group is optionally substituted with 1 to 3 groups independently selected from halogen, -CF₃, -OCF₃, hydroxyl, or methoxy;

(P) R²⁴ is selected from: hydrogen, alkyl, -SO₂R²², or aryl, wherein said aryl group is optionally substituted with 1 to 3 groups independently selected from halogen, -CF₃, -OCF₃, hydroxyl, or methoxy;

(Q) a is 0 to 2;

(R) b is 0 to 2;

(S) k is 1 to 5;

(T) m is 2 to 5;

- 9 -

- (U) n is 1, 2 or 3 with the proviso that when M¹ is N, then n is not 1;
- (V) p is 1, 2 or 3 with the proviso that when M² is N, then p is not 1;
- (W) q is 1 to 5; and
- (X) r is 1, 2, or 3 with the proviso that when r is 2 or 3, then M² is C and p is 1.

This invention also provides a pharmaceutical composition comprising an effective amount of compound of Formula I, and a pharmaceutically acceptable carrier.

This invention further provides a method of treating: allergy, allergy-induced airway (e.g., upper airway) responses, congestion (e.g., nasal congestion), hypotension, cardiovascular disease, hypotension, diseases of the GI tract, hyper and hypo motility and acidic secretion of the gastro-intestinal tract, obesity, sleeping disorders (e.g., hypersomnia, somnolence, and narcolepsy), disturbances of the central nervous system, attention deficit hyperactivity disorder ADHD), hypo and hyperactivity of the central nervous system (for example, agitation and depression), and/or other CNS disorders (such as Alzheimer's, schizophrenia, and migraine) comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I.

This invention further provides a method of treating: allergy comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I.

This invention further provides a method of treating: allergy-induced airway (e.g., upper airway) responses comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I.

This invention further provides a method of treating: congestion (e.g., nasal congestion) comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I.

This invention further provides a pharmaceutical composition comprising an effective amount of a compound of Formula I, and an effective amount of a H₁ receptor antagonist in combination with a pharmaceutically acceptable carrier.

This invention further provides a method of treating: allergy, allergy-induced airway (e.g., upper airway) responses, and congestion (e.g., nasal congestion)

- 10 -

comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I in combination with an effective amount of an H₁ receptor antagonist.

This invention further provides a method of treating: allergy comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I in combination with an effective amount of an H₁ receptor antagonist.

This invention further provides a method of treating: allergy-induced airway (e.g., upper airway) responses comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I in combination with an effective amount of an H₁ receptor antagonist.

This invention further provides a method of treating: congestion (e.g., nasal congestion) comprising administering to a patient in need of such treatment (e.g., a mammal, such as a human being) an effective amount of a compound of Formula I in combination with an effective amount of an H₁ receptor antagonist.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms have the following meanings, unless indicated otherwise:

alkyl-(including the alkyl portions of alkylamino, alkylaryl, arylalkyl, alkoxy and dialkylamino)-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms;

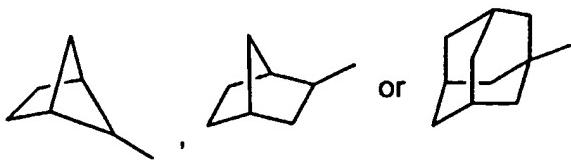
alkylaryl-represents an alkyl group, as defined above, bound to an aryl group, as defined below, wherein said aryl group is bound to the compound;

aryl (including the aryl portion of alkylaryl and arylalkyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl or naphthyl ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally substituted with one or more (e.g., 1 to 3) substituents independently selected from: halo, alkyl, hydroxy, alkoxy, phenoxy, CF₃, amino, alkylamino, dialkylamino, -COOR²⁰ or -NO₂;

arylalkyl-represents an aryl group, as defined above, bound to an alkyl group, as defined above, wherein said alkyl group is bound to the compound;

- 11 -

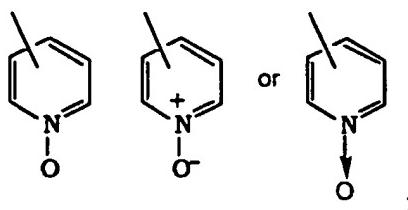
bridged bicyclic cycloalkyl rings-represents a cycloalkyl ring, as defined below, having an alkyl (as defined above) bridge from one ring carbon to another ring carbon thereby forming a bicyclic cycloalkyl ring, e.g.,



cycloalkyl-represents saturated carbocyclic rings of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms;

halo (halogen)-represents fluoro, chloro, bromo and iodo; and

heteroaryl-represents cyclic groups, having at least one heteroatom selected from O, S or N, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups preferably containing from 2 to 14 carbon atoms; examples include but are not limited to isothiazolyl, isoxazolyl, oxazolyl, furazanyl, triazolyl, thiazolyl, thienyl, furanyl (furyl), pyrrolyl, pyrazolyl, pyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyridyl (e.g., 2-, 3-, or 4-pyridyl), pyridyl N-oxide (e.g., 2-, 3-, or 4-pyridyl N-oxide), triazinyl, pteridinyl, indolyl (benzopyrrolyl), pyridopyrazinyl, isoquinolinyl, quinolinyl, naphthyridinyl, wherein said pyridyl N-oxide can be represented as:



heterocycloalkyl-represents a saturated, carbocyclic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero groups selected from -O-, -S-, -SO-, -SO₂ or -NR⁴⁰, wherein R⁴⁰ represents H, C₁ to C₆ alkyl, arylalkyl, -C(O)R²⁰, -C(O)OR²⁰, or -C(O)N(R²⁰)₂ (wherein each R²⁰ is independently selected); examples include but are not limited to 2- or 3-tetrahydrofuranyl, 2- or 3-tetrahydrothienyl, 2-, 3- or 4-piperidinyl, 2- or 3-pyrrolidinyl, 2- or 3-piperizinyl, 2- or 4-dioxanyl, 1,3-dioxolanyl, 1,3,5-trithianyl, pentamethylene sulfide, perhydroisoquinolinyl, decahydroquinolinyl, trimethylene oxide, azetidinyl, 1-azacycloheptanyl, 1,3-dithianyl, 1,3,5-trioxanyl,

- 12 -

morpholinyl, thiomorpholinyl, 1,4-thioxanyl, and 1,3,5-hexahydrotriazinyl, thiazolidinyl, tetrahydropyranyl;

heterocycloalkylheteroaryl-represents a heteroaryl group as defined above bound to a heterocycloalkyl as defined above;

lower alkyl-represents an alkyl group, as defined above, that comprises 1 to 6 carbon atoms, preferably 1-4 carbon atoms;

lower alkoxy-represents an alkoxy group whose alkyl moiety comprises 1 to 6 carbon atoms, preferably 1-4 carbon atoms;

Ac-represents acetyl (i.e.,CH₃C(O)-);

t-BOC-represents t-butyloxycarbonyl;

Ci/mmol-represents curie/mmol (a measure of specific activity);

DCC-represents dicyclohexylcarbodiimide;

DEC-represents 2-diethylaminoethyl chloride hydrochloride;

DIC-represents diisopropylcarbodiimide;

DMF-represents dimethylformamide;

DMSO-represents dimethylsulfoxide;

EtOAc-represents ethyl acetate;

EtOH-represents ethanol;

FMOC-represents 9-fluorenylmethoxycarbonyl;

HOBT-represents 1-hydroxybenzotriazole;

Ki-represents inhibition constant for substrate/receptor complex;

LiOH-represents lithium hydroxide;

Me-represents methyl;

MeOH-represents methanol;

nM-represents nanomolar;

PyBOP-represents benzotriazole-1-yl-oxy-trispyrrolidino-phosphonium hexafluorophosphate;

TFA-represents trifluoroacetic acid;

THF-represents tetrahydrofuran;

Also, as used herein, "upper airway" usually means the upper respiratory system--i.e., the nose, throat, and associated structures.

Also, as used herein, "effective amount" generally means a therapeutically effective amount.

- 13 -

Lines drawn into the rings indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers, diastereoisomers and geometric) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

The compounds of this invention are ligands for the histamine H₃ receptor. The compounds of this invention can also be described as antagonists of the H₃ receptor, or as H₃ antagonists.

The compounds of the invention are basic and form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for such salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their corresponding salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their corresponding free base forms for purposes of this invention.

The compounds of Formula I can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemi-hydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

The compounds of this invention can be combined with an H₁ receptor antagonist (i.e., the compounds of this invention can be combined with an H₁ receptor antagonist in a pharmaceutical composition, or the compounds of this invention can be administered with H₁ receptor antagonist).

Numerous chemical substances are known to have histamine H₁ receptor antagonist activity and can therefore be used in the methods of this invention. Many H₁ receptor antagonist useful in the methods of this invention can be classified as ethanolamines, ethylenediamines, alkylamines, phenothiazines or piperidines.

- 14 -

Representative H₁ receptor antagonists include, without limitation: astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine (also known as SCH-34117), diphenhydramine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, meclizine, mizolastine, mequitazine, mianserin, noberastine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripeleannamine, temelastine, trimeprazine and tripolidine. Other compounds can readily be evaluated to determine activity at H₁ receptors by known methods, including specific blockade of the contractile response to histamine of isolated guinea pig ileum. See for example, WO98/06394 published February 19, 1998.

Those skilled in the art will appreciate that the H₁ receptor antagonist is used at its known therapeutically effective dose, or the H₁ receptor antagonist is used at its normally prescribed dosage.

Preferably, said H₁ receptor antagonist is selected from: astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, diphenhydramine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, meclizine, mizolastine, mequitazine, mianserin, noberastine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripeleannamine, temelastine, trimeprazine or tripolidine.

More preferably, said H₁ receptor antagonist is selected from: astemizole, azatadine, azelastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, carebastine, descarboethoxyloratadine, diphenhydramine, doxylamine, ebastine, fexofenadine, loratadine, levocabastine, mizolastine, norastemizole, or terfenadine.

Most preferably, said H₁ receptor antagonist is selected from: azatadine, brompheniramine, cetirizine, chlorpheniramine, carebastine, descarboethoxy-loratadine (also known as SCH-34117), diphenhydramine, ebastine, fexofenadine, loratadine, or norastemizole.

Even more preferably, said H₁ antagonist is selected from: loratadine, descarboethoxyloratadine, fexofenadine or cetirizine. Still even more preferably, said H₁ antagonist is loratadine or descarboethoxyloratadine.

- 15 -

In one preferred embodiment, said H₁ receptor antagonist is loratadine.

In another preferred embodiment, said H₁ receptor antagonist is descarboethoxyloratadine.

In still another preferred embodiment, said H₁ receptor antagonist is fexofenadine.

In yet another preferred embodiment, said H₁ receptor antagonist is cetirizine.

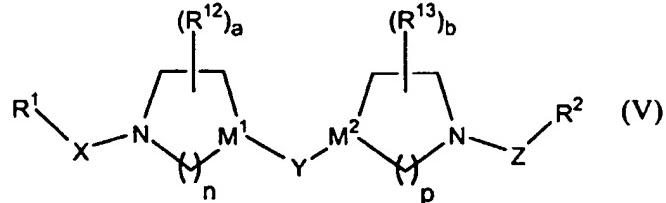
Preferably, in the above methods, allergy-induced airway responses are treated.

Also, preferably, in the above methods, allergy is treated.

Also, preferably, in the above methods, nasal congestion is treated.

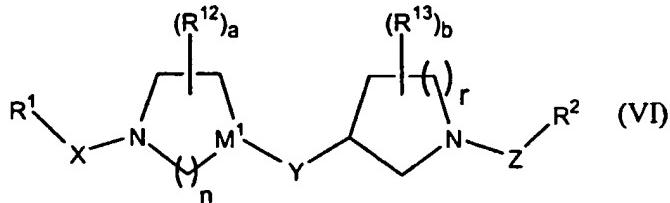
In the methods of this invention wherein a combination of an H₃ antagonist of this invention (compound of Formula I) is administered with a H₁ antagonist, the antagonists can be administered simultaneously, consecutively (one after the other within a relatively short period of time), or sequentially (first one and then the other over a period of time). In general, when the antagonists are administered consecutively or sequentially, the H₃ antagonist of this invention (compound of Formula I) is administered first.

Compounds of Formula I include compounds of the formula:



wherein R¹, X, n, M¹, R¹², a, Y, M², R¹³, b, p, Z and R² are as defined for Formula I.

Compounds of Formula I also include compounds of the formula:



wherein R¹, X, n, M¹, R¹², a, Y, R¹³, b, r, Z and R² are as defined for Formula I.

R¹ is preferably selected from:

- (1) substituted aryl, more preferably substituted phenyl;
- (2) substituted heteroaryl, more preferably substituted isoxazolyl; or

- 16 -

- (3) formula IVA wherein each R³ is independently selected, more preferably each R³ is alkyl, most preferably each R³ is C₁ to C₄ alkyl, even more preferably each R³ is the same moiety, and still more preferably each R³ is methyl.

Preferably, when R¹ is a substituted phenyl group, the phenyl group has 1 to 3 substituents and the substituents are independently selected from:

- (1) -C(O)N(R⁴)₂, preferably each R⁴ is independently selected, more preferably each R⁴ is independently selected from H or arylalkyl (e.g., -CH₂CH₂phenyl), most preferably one R⁴ is H and the other is arylalkyl, even more preferably one R⁴ is H and the other R⁴ is -CH₂CH₂phenyl;
- (2) halo, more preferably 1 to 3 halos independently selected from Br, Cl and F;
- (3) -S(O)₂R²², more preferably R²² is heterocycloalkyl, most preferably R²² is morpholinyl or pyrrolidinyl;
- (4) -OCF₃;
- (5) -OCHF₂; or
- (6) -S(O)₂N(R²⁰)₂, more preferably each R²⁰ is independently selected from alkyl or substituted phenyl, most preferably C₁ to C₄ alkyl or halo substituted phenyl, even more preferably methyl or chlorophenyl; still more preferably each R²⁰ is methyl or one R²⁰ is methyl and the other R²⁰ is chlorophenyl.

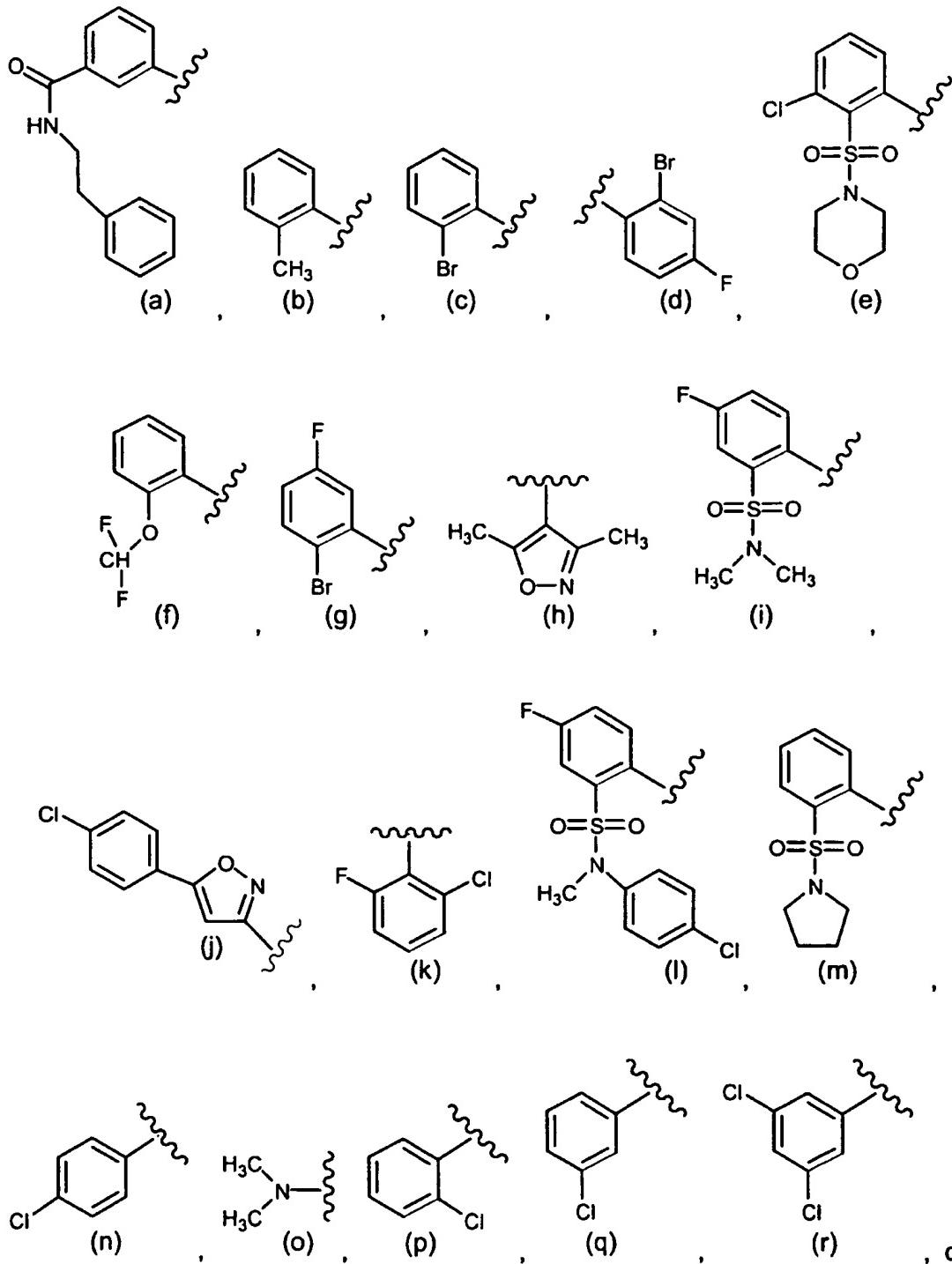
Preferably, when R¹ is a substituted isoxazolyl group the isoxazolyl group has 1 or 2 substituents independently selected from:

- (1) alkyl, more preferably C₁ to C₄ alkyl, most preferably methyl; or
- (2) substituted phenyl, more preferably halo substituted phenyl (1 to 3 halo groups, preferably one halo group), most preferably chloro substituted phenyl (e.g., chlorophenyl).

More preferably the isoxazolyl is substituted with two alkyl groups (most preferably two methyl groups), or one halophenyl group (most preferably chlorophenyl).

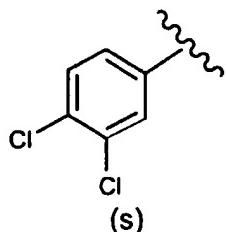
Examples of R¹ groups include but are not limited to:

- 17 -



, or

- 18 -



Preferably X is selected from $-\text{CH}_2-$ (i.e., q is preferably 1) or $-\text{SO}_2-$. More preferably X is $-\text{CH}_2-$.

Preferably n is 2.

Preferably M¹ is N.

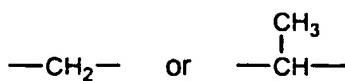
Preferably Y is $-\text{C}(\text{O})-$.

Preferably M² is C.

Preferably p is 2.

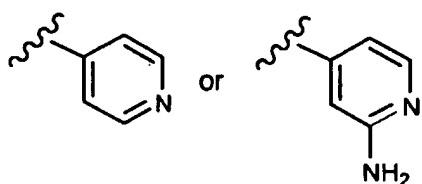
Preferably r is 1.

Preferably Z is a C₁ to C₆ alkyl group. More preferably Z is

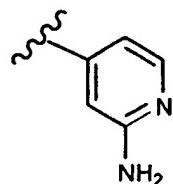


Most preferably Z is $-\text{CH}_2-$.

Preferably R² is a six membered heteroaryl ring or a substituted six membered heteroaryl ring, and more preferably the heteroaryl ring contains one nitrogen atom. Preferably the substituted heteroaryl ring is substituted with one $-\text{NR}^4\text{R}^5$, and more preferably the substituent is $-\text{NH}_2$. Most preferably R² is selected from



Even more preferably R² is



Preferably a is 0 and therefore there is no R¹² group present.

Preferably b is 0 or 1, more preferably 0. When b is 1 R¹³ is preferably $-\text{OH}$. More preferably, when b is 1, R¹³ is $-\text{OH}$ bound to the M² substituent and M² is C.

- 19 -

Representative compounds of this invention include, but are not limited to: Compounds 18 (Example 1), 25 (Example 2), 26 (Example 3), 31 (Example 4), 33 (Example 5), 37 (Example 6), 41 (Example 7), 45 (Example 8), 49 (Example 9), 51 (Example 10), 52 (Example 11), 57 (Example 12), 58 to 67, 73 to 84, 89 to 157, 159 to 168, 212 to 269, 271 to 272, 276 to 282, 284, 285, 287 to 300, 306, 309 to 319, 321 to 336, 338 to 340, 342 to 349, 351 to 361, 363 to 371, 374 to 377, 380 to 383, 387 to 390, 392 to 406, and 408 to 410.

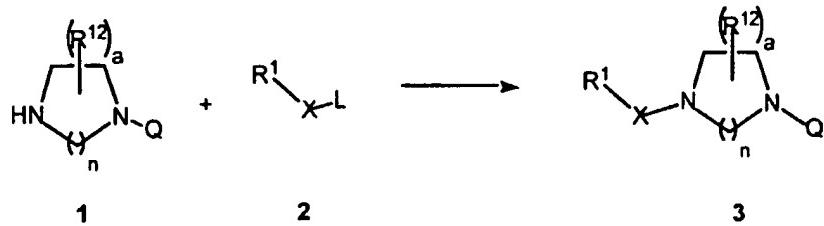
Preferred compounds are Compounds 93, 276, 306, 317, 331, 332, 333, 336, 366, 343, 366, 367, 374, and 376

More preferred compounds are Compounds 306, 332, 333, 336, 366, 374, and 376.

Structures for the above compounds are given below.

The following processes may be employed to produce compounds of the invention.

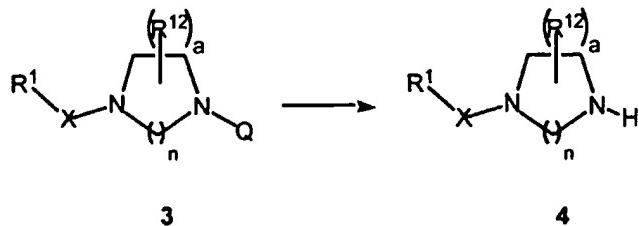
Step 1



In Step 1, compound 1, in which Q is a protecting group such as a carbamate, amide, or a substituted benzylic group, is allowed to react with compound 2, in which L is a leaving group such as a halogen atom, in a suitable solvent such as THF, DMSO or DMF in the presence of a base such as a tertiary amine or an inorganic base such as Na₂CO₃ at a temperature sufficient to achieve a reasonable reaction rate. R¹², M¹, n, a, R¹, and X are as defined above. Alternatively, in the case when X is -(CH₂)_q-, L can equal an aldehyde group, CHO and X is -(CH₂)_{q-1}-. In that case, compounds 1 and 2 are combined in a solvent such as trifluoroethanol in the presence of sieves. A reducing agent, such as NaBH(OAc)₃ or NaCNBH₃ is added and the reaction stirred at a temperature suitable to complete the reaction.

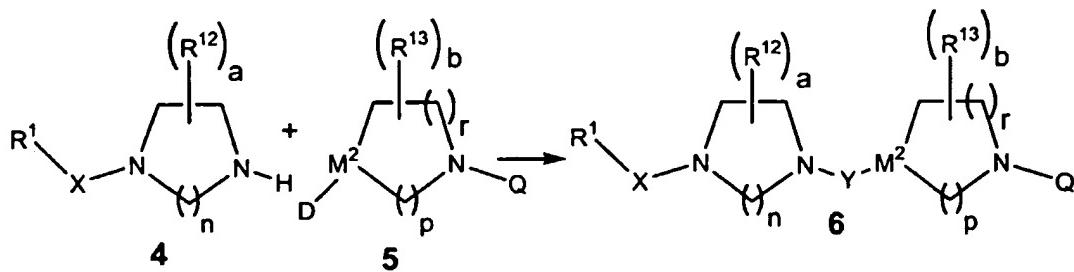
- 20 -

Step 2



In Step 2, the protecting group Q is removed. When said protecting group is a carbamate such as t-BOC, dilute acid is used. In the case of a benzyl group, catalytic hydrogenation is used.

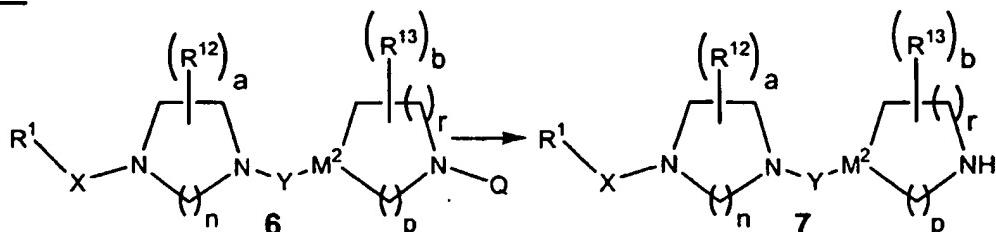
Step 3



When Y is C=O, amine 4 can be coupled to acid 5 (D is CO₂H, M² is carbon) using a number of methods well known in the art such as DCC or PyBOP.

Alternatively, the acid 5 can be activated by conversion to the acid chloride or mixed anhydride and then reacted with the amine 4 to give 6. Suitable protecting groups for 5 include t-Boc or the like. Alternatively, when Y is -CH₂- and M² is carbon, D can be -CH₂-L (where L is a halogen) and the reaction can be performed as in Step 1.

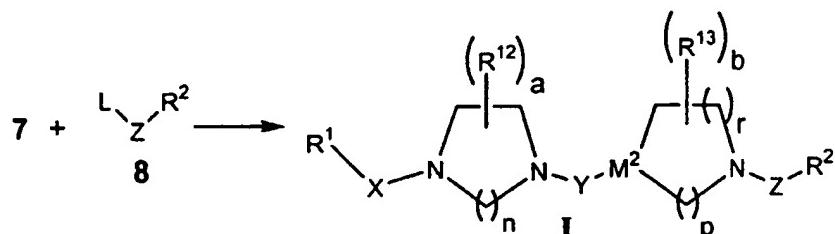
Step 4



Compound 6 in which the protecting group is a t-Boc can be deprotected under acidic conditions such as HCl in dioxane or TFA in CH₂Cl₂ to give the amine 7.

Step 5

- 21 -



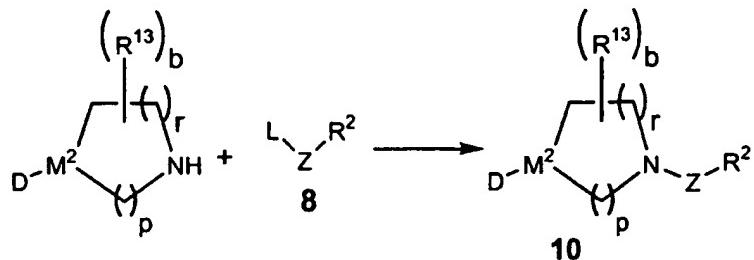
The amine 7 can be alkylated by reaction with the electrophile 8. In one case, L represents a carbonyl group and Z is a branched or straight chain alkyl group. Compounds 7 and 8 are combined in a solvent such as CH_2Cl_2 in the presence of sieves. After a suitable amount of time, a reducing agent such as $\text{NaBH}(\text{OAc})_3$ is added to give the product I. Alternatively, when L is a halogen atom such as Cl or Br, and Z is a branched or straight chain alkyl group or $-\text{SO}_2-$ 7 and 8 are combined in a solvent such as DMF in the presence of a tertiary amine base to give the product I.

Alternative Synthesis

An alternative approach to the synthesis of compounds of Formula I is given below.

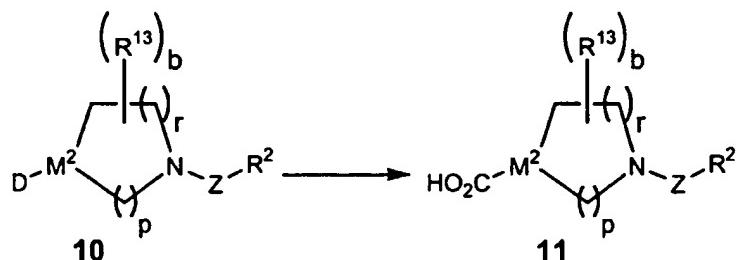
- 22 -

St p 1



In the same manner as Step 5, compounds 8 and 9 can be converted to 10. In the case when M^2 is carbon, D is CO_2alkyl and when M^2 is nitrogen, D is a protecting group such as the BOC group.

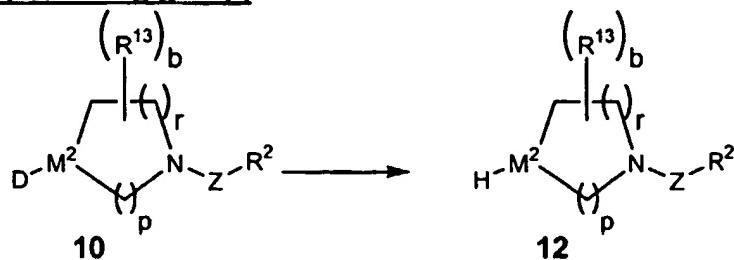
Step 2



Compound 10 (D is CO_2alkyl) is saponified in a mixed solvent such as EtOH or MeOH and water, or THF, water, and MeOH using an alkali metal base such as LiOH or NaOH at a temperature of from 50 to 100°C to give 11.

Compound 11 can be combined with compound 4 as described in Step 3.

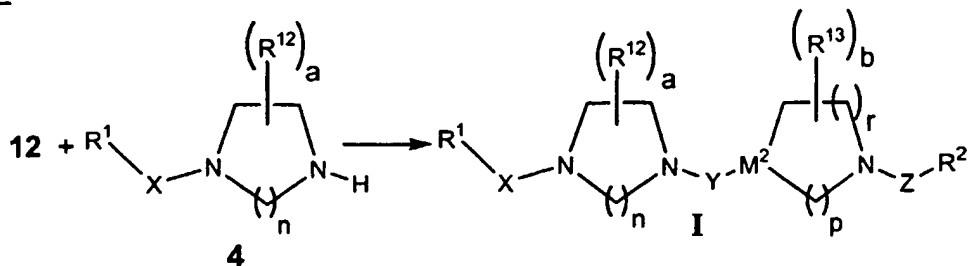
Step 3 (D is a protecting group)



Compound 10, in which D is a protecting group such as t-Boc and M^2 is nitrogen, can be deprotected under acidic conditions such as HCl in dioxane or TFA in CH_2Cl_2 to give the amine 12.

- 23 -

St p 4



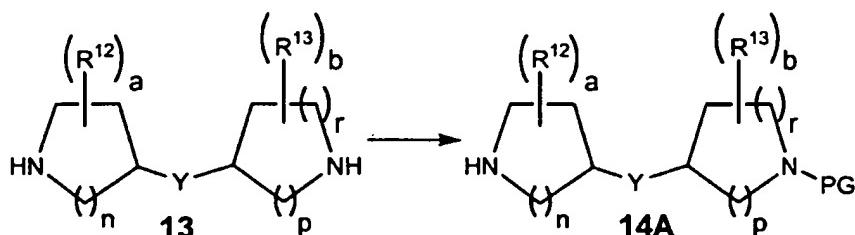
Compound 12 can be coupled with compound 4 using a reagent such as carbonyl diimidazole or the like in a solvent such as THF, ether or the like at a temperature from 0 to 60°C to give compound I (Y is C=O, M^1 and M^2 are nitrogen).

Step 5

Compound I (Y is C=O) can be converted to compound I (Y is C=S) by treatment of I with a reagent such as Lawesson's reagent in a solvent such as toluene at a temperature from 20 to 100°C.

Synthesis (M^1 and M^2 are carbon)

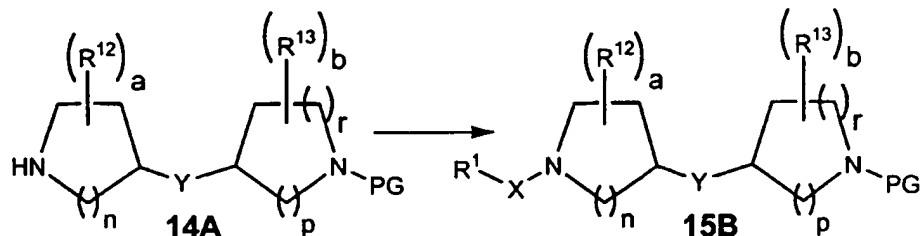
Step 1



A solution of an excess of 13 in a solvent such as THF, CH_2Cl_2 or the like is treated with a reagent such as BOC_2O or an acid chloride or anhydride at a temperature of from $-20^\circ C$ to $+30^\circ C$ to produce 14A in which PG is a BOC group, or an amide. Alternatively, a solution of an excess of 13 in a solvent such as THF, CH_2Cl_2 or the like is treated with a substituted or unsubstituted benzyl bromide in the presence of a base such as triethylamine to give 14A in which PG is a substituted benzyl group.

- 24 -

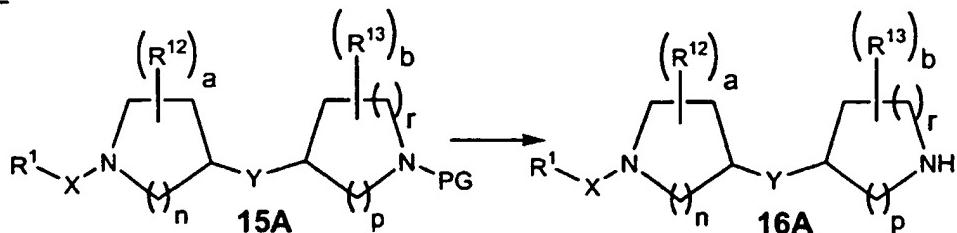
Step 2



In Step 2, compound 14A, in which PG is a protecting group such as a carbamate, amide, or a substituted benzylic group, is allowed to react with compound 2, in which L is a leaving group such as a halogen atom, in a suitable solvent such as THF, DMSO or DMF in the presence of a base such as a tertiary amine or an inorganic base such as Na₂CO₃ at a temperature sufficient to achieve a reasonable reaction rate to give compound 15A. R¹², R¹³, M¹, n, p, a, b, r, R¹, and X are as defined for formula I. Alternatively, in the case when X is -(CH₂)_q-, L can equal an aldehyde group, CHO, and X is -(CH₂)_{q-1}-.

In that case, compounds 14A and 2 are combined in a solvent such as trifluoroethanol in the presence of sieves and stirred for a suitable time. A reducing agent, such as NaBH(OAc)₃ or NaCNBH₃ is added and the mixture stirred at a temperature suitable to complete the reaction.

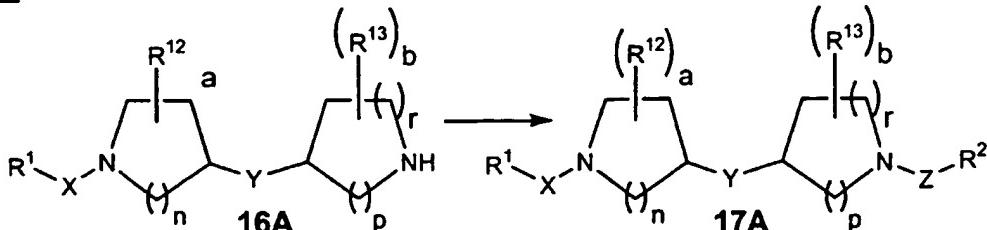
Step 3



Compound 15A in which the protecting group is t-Boc can be deprotected under acidic conditions such as HCl in dioxane or TFA in CH₂Cl₂ to give the amine 16A. Alternatively, when PG is a benzyl group, it can be removed by catalytic hydrogenation using a catalyst such as Pd/C.

- 25 -

Step 4

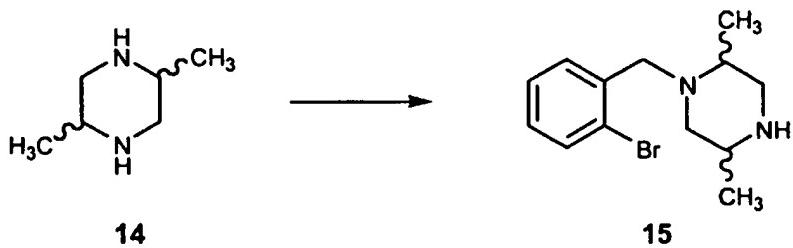


The amine **16A** can be alkylated by reaction with the electrophile **8**. In one case, L represents a carbonyl group and Z is a branched or straight chain alkyl group. Compounds **16A** and **8** are combined in a solvent such as CH_2Cl_2 in the presence of sieves. After a suitable amount of time, a reducing agent such as $\text{NaBH}(\text{OAc})_3$ is added to give the product **17A**. Alternatively, when L is a halogen atom such as Cl or Br, and Z is a branched or straight chain alkyl group or $-\text{SO}_2-$ **16A** and **8** are combined in a solvent such as DMF in the presence of a tertiary amine base to give the product **17A**.

Compounds useful in this invention are exemplified by the following examples which should not be construed as limiting the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

Example 1

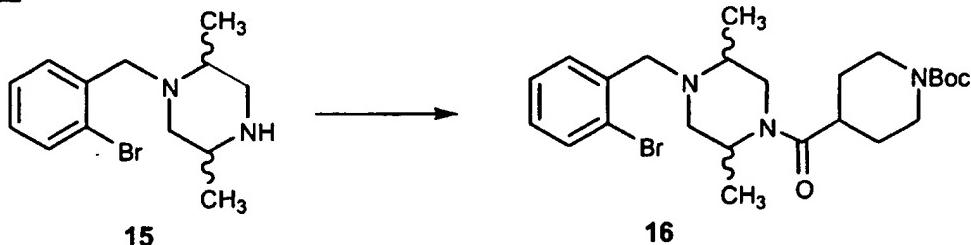
Step 1:



Compound **14** (5 g, 43.8 mmol) and 2-bromobenzaldehyde (4.1 g, 22.2 mmol) were combined in CH_2Cl_2 (130 mL) and stirred for 2 h. $\text{Na}(\text{OAc})_3\text{BH}$ (6.4 g, 30.2 mmol) was added and the mixture stirred overnight at room temperature. The reaction was then washed with saturated NaHCO_3 and brine and dried. Filtration and concentration gave a residue which was purified by flash column chromatography (5% to 10% MeOH/ NH_3 in CH_2Cl_2) to give **15** (3.44 g, 55%) Mass spectrum = 453 ($\text{M}+\text{H}$).

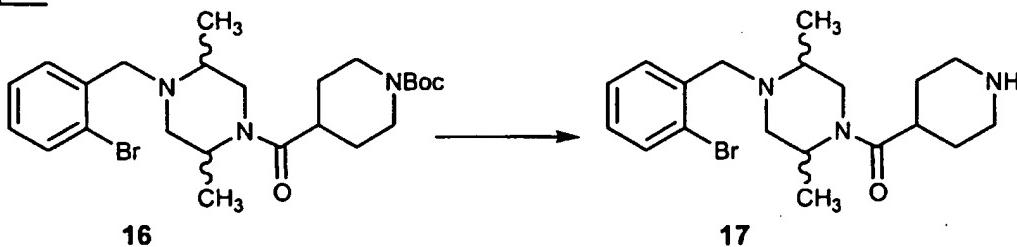
- 26 -

Step 2:



A solution of **15** (2 g, 7.06 mmol), N-Boc isonipecotic acid (1.47 g, 6.42 mmol) and PyBOP (3.34 g, 6.42 mmol) in CH₂Cl₂ (20 mL) was cooled to 0°C and diisopropyl ethyl amine (2.49 g, 19.3 mmol) was added. After 1 minute, the cooling bath was removed and the reaction stirred at room temperature for 48 hours. The reaction was washed with saturated NaHCO₃, dried (Na₂SO₄), and concentrated and the residue was purified by flash column chromatography (30% to 50 % ethyl acetate in hexane) to give **16** (3 g, 60%).

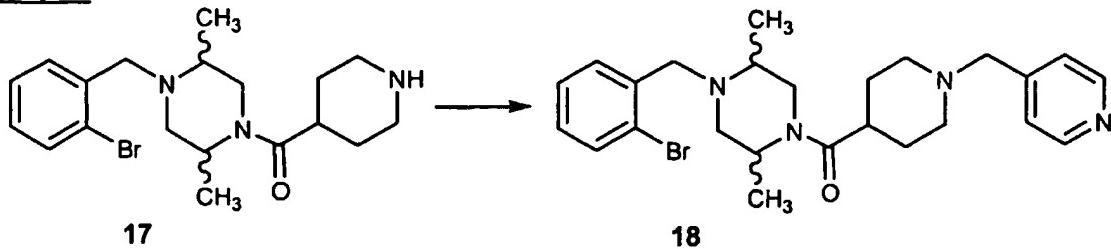
Step 3:



A solution of **16** (3 g, 6.07 mmol) in CH₂Cl₂ (100 mL) at 0° C was treated with 4 N HCl (8 mL) and the reaction stirred at room temperature overnight. The solvent was removed in vacuo and the residue was dissolved in water and the pH adjusted to 8 by addition of aqueous NaOH. The water was removed in vacuo and the residue dissolved in MeOH, filtered and concentrated to give **17** as a white solid (3 g, >100%) which was used as is. Mass spectrum: 394 (M+H).

- 27 -

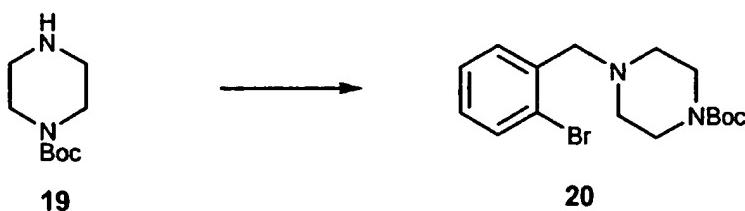
Step 4:



In a manner similar to that described in Example 1, Step 1, **17** (0.95 g, 2.4 mmol) and pyridine-4-carboxaldehyde (0.22 g, 2.02 mmol) was converted to **18** (0.57 g, 58%). Mass spectrum: 485 (M+H).

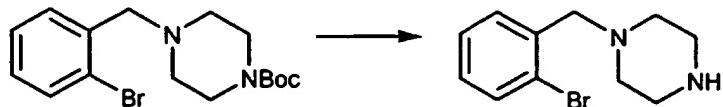
Example 2

Step 1:



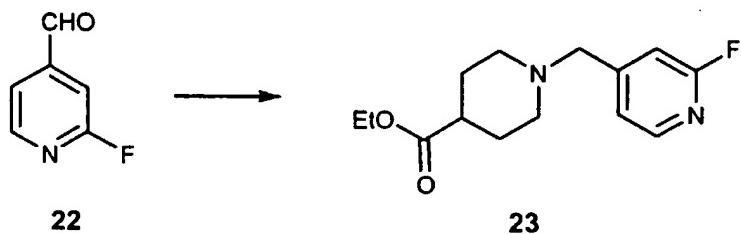
In a manner similar to that described in Example 1, Step 1, **19** (5 g, 26 mmol) and 2-bromobenzaldehyde (4.1 g, 21.7 mmol) was converted to **20** (6.2 g, 80%).

Step 2:



In a manner similar to that described in Example 1, Step 3, **20** (6.2 g, 17.5 mmol) was converted to **21** (5.5 g, 100%).

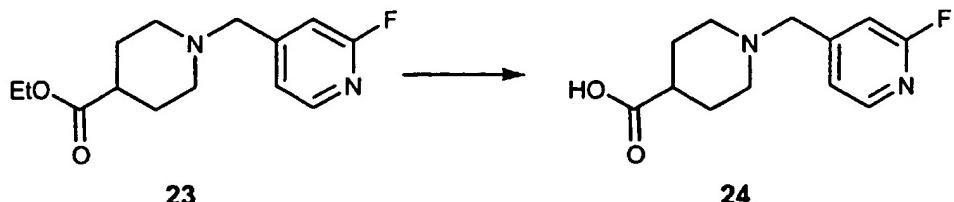
Step 3



- 28 -

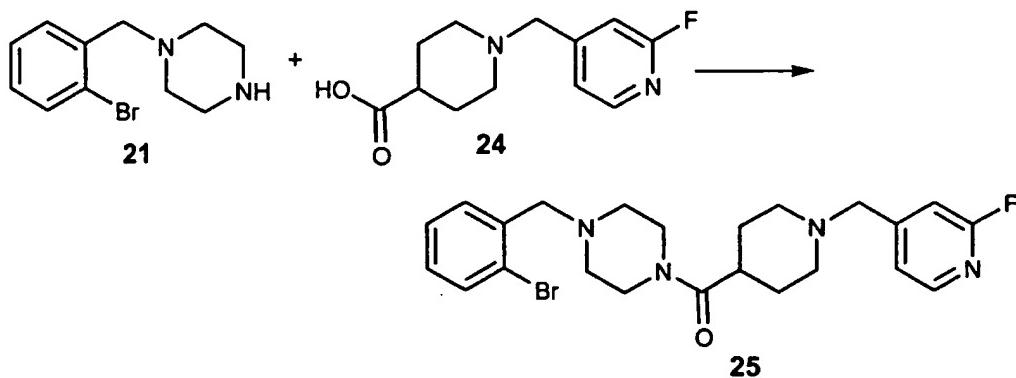
In a manner similar to that described in Example 1, Step 1, **22** (0.45 g, 3.6 mmol) and ethyl isonipecotate (0.7, 4.4 mmol) were converted to **23** (0.45 g, 64%).

Step 4:



A solution of **23** (0.45 g, 1.69 mmol) in MeOH (10 mL) was treated with 1 N KOH (5 mL) and the mixture was heated to 60° C overnight. The reaction was cooled and concentrated. The residue was dissolved in water and extracted with ethyl acetate. The pH of the aqueous phase was adjusted to 6-7 by addition of 1N HCl. The water was removed in vacuo and the residue taken up in MeOH, filtered and concentrated to give **24** which was used in the next step as is.

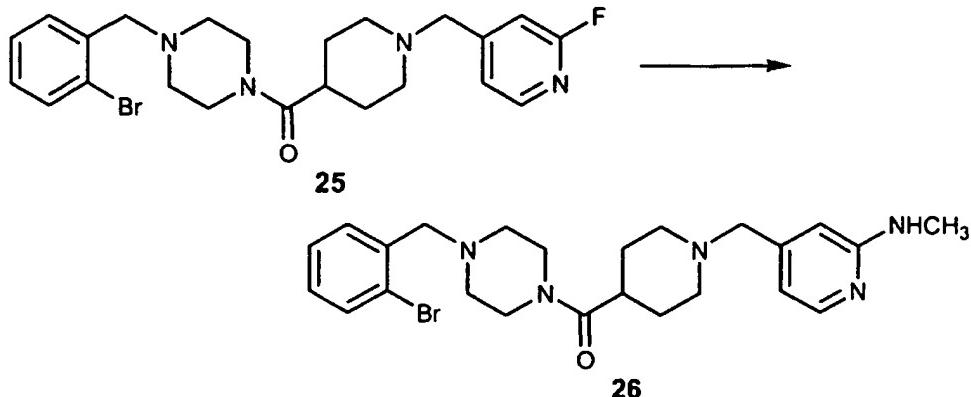
Step 5:



In a manner similar to that described in Example 1, Step 2, **21** (0.35 g, 1.39 mmol) and **24** (0.3 g, 1.26 mmol) was converted to **25** (0.50 g, 66%). Mass spectrum: 475 (M+H).

- 29 -

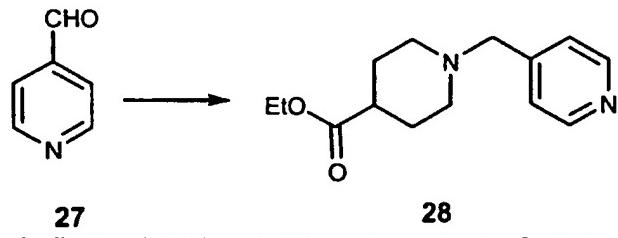
Example 3



To a solution of **25** (0.11 g, 0.23 mmol) in 2-propanol (6 mL) in a pressure vessel was added triethylamine (7 mL) and methylamine hydrochloride (3 g, 44.4 mmol) and the reaction heated to 95°C for 6 days. The reaction was cooled and the solvent removed in *vacuo*. The residue was dissolved in ethyl acetate and washed with half saturated NaHCO₃. The organic layer was dried and concentrated, and the residue purified on a flash column (20% MeOH in ethyl acetate) to give **26** (40 mg, 36%). Mass spectrum: 486 (M+H).

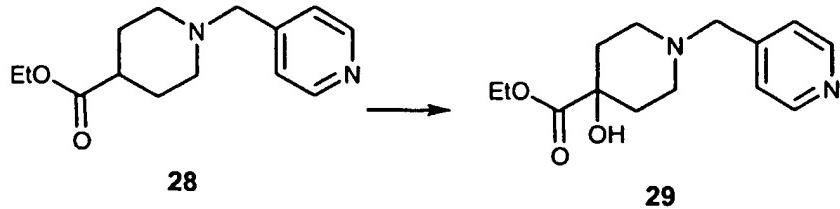
Example 4

Step 1:



In a manner similar to that described in Example 1, Step 1, **27** (2 g, 18.3 mmol) and ethyl isonicotinate (3.5, 22 mmol) were converted to **28** (4.5 g, 99%).

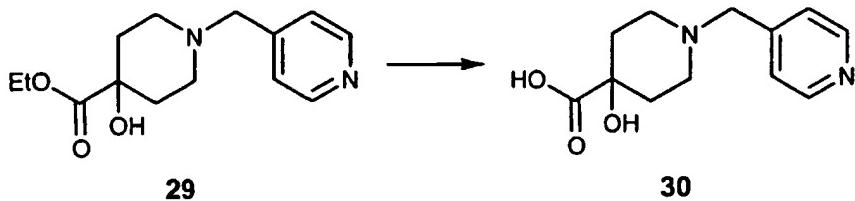
Step 2:



- 30 -

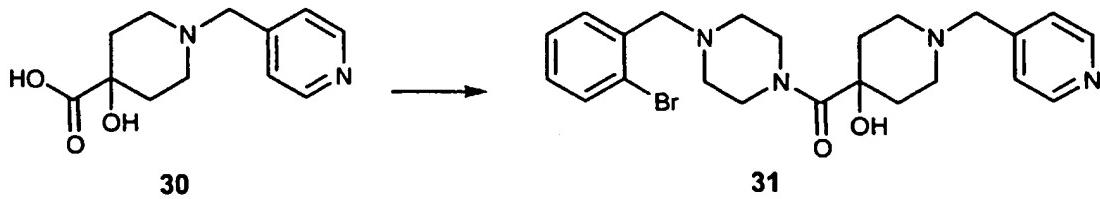
A solution of n-BuLi (3 mL of a 1.6 M solution in hexane, 4.8 mmol) in THF (25 mL) was treated at – 25° C with (i-Pr)₂NH (0.49 g, 4.8 mmol). The reaction was stirred for 1 h at 0°C and then cooled to – 70° C. Compound **28** (1.0 g, 4 mmol) in THF (3 mL) was added dropwise and the reaction stirred at – 70°C for 2 h and – 50° C for 2 h. The reaction was recooled to – 70° C and (1S)-(+)-(10-camphorsulfonyl)oxaziridine (1.04 g, 4.52 mmol) in THF (10 mL) was added. The reaction was stirred at – 70° C for 2 h and slowly warmed to room temperature overnight. The reaction was quenched by the addition of saturated aqueous NH₄Cl and extracted with EtOAc. The organic layer was dried and concentrated, and the residue purified by column chromatography (4% MeOH in ethyl acetate) to give **29** (0.75 g, 71%).

Step 3:



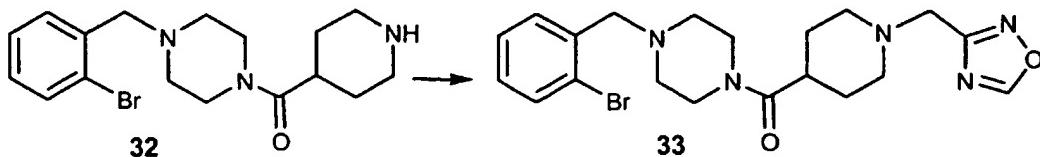
In a manner similar to that described in Example 2, Step 4, **29** (0.35 g, 1.32 mmol) was converted to **30** (0.32 g, 99%).

Step 4:



In a manner similar to that described in Example 1, Step 2, **30** (0.2 g, 0.85 mmol) was converted to **31** (0.10 g, 25%). Mass spectrum: 473 (M+H).

Example 5

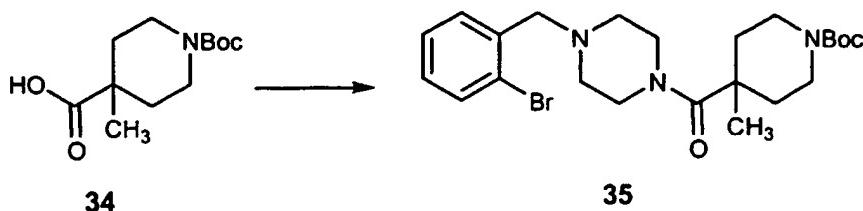


- 31 -

To a solution of **32** (0.52 g, 1.43 mmol; synthesized in the same manner as compound **17**) and 3-chloromethyloxadiazole (0.25g, 2.11 mmol) in toluene (10 mL) was added triethylamine (0.6 mL) and the reaction was heated to 75° C overnight. The reaction was cooled, diluted with ethyl acetate and washed with saturated NaHCO₃. The organic layer was dried and concentrated and the residue purified by flash column chromatography (10% MeOH in ethyl acetate) to give **33** (0.2 g, 31%) Mass spectrum: 448 (M+H).

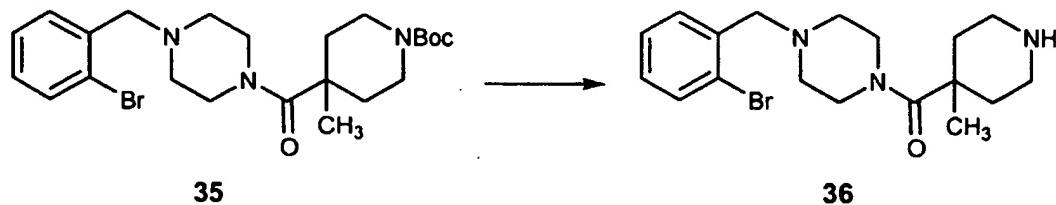
Example 6

Step 1



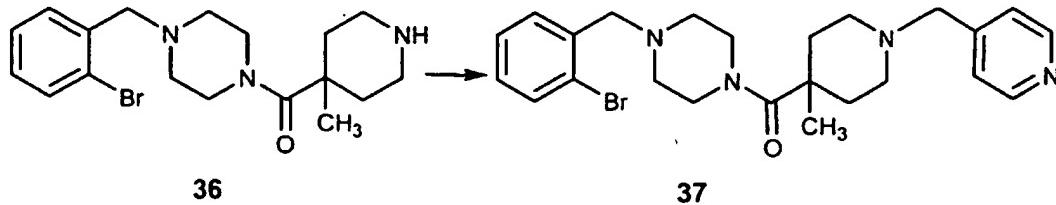
In a manner similar to that described in Example 1, Step 2, compound **34** (1.2 g, 4.93 mmol) was coupled with compound **21** (1.4 g, 5.43 mmol) to give compound **35** (1.7 g, 74%).

Step 2



In a manner similar to that described in Example 1, Step 3, compound **35** (1.7 g, 3.54 mmol) was converted to **36** (1.3 g, 97%).

Step 3

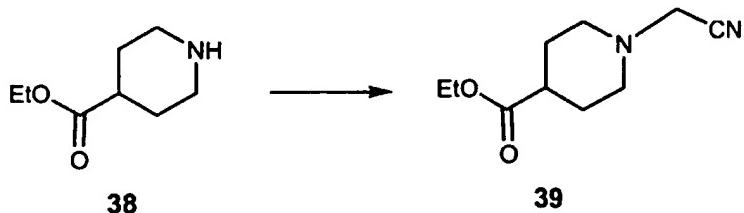


- 32 -

In a manner similar to that described in Example 1, Step 1, compound 36 (0.41 g, 1.08 mmol) was converted to 37 (0.2 g, 45%). Mass Spectrum : 471 (M+H).

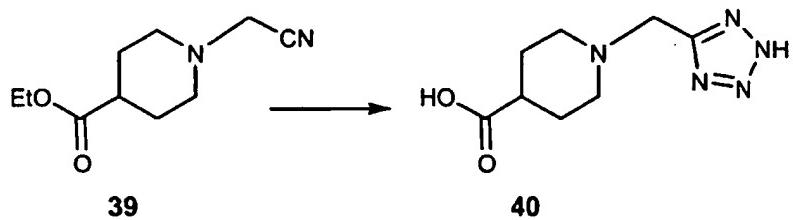
Example 7

Step 1



To a stirred mixture of 38 (2.0 g, 12.5 mmol) and Na₂CO₃ (1.45 g, 13.7 mmol) in acetone (15 mL) was added chloroacetonitrile (1.05 g, 13.7 mmol) and the reaction mixture stirred for 3 h at room temperature. The solvent was removed in vacuo and the residue partitioned between ethyl acetate and water. The ethyl acetate layer was dried (Na₂SO₄) and concentrated to give 37 (2.3 g, 94%) which was used as is.

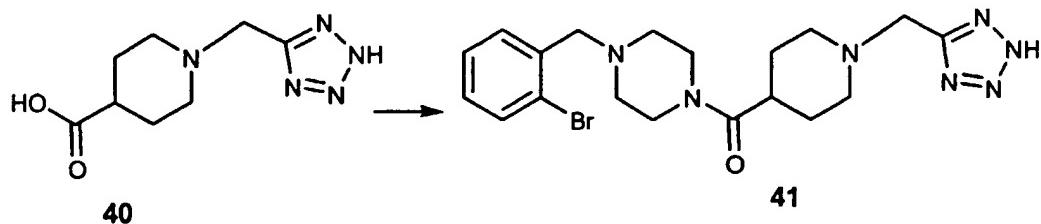
Step 2



To a solution of 39 (2.2 g, 11.2 mmol) in toluene (20 mL) was added n-Bu₃Sn (5.7 g, 16.8 mmol) and the reaction heated to reflux for 48 h. Additional n-Bu₃Sn (0.5 mL) was added and the reaction was stirred at reflux for 6 h and at room temperature for 18 h. The reaction was cooled to room temperature, 5 N NaOH (35 mL) and hexane (35 mL) were added and the reaction was stirred for 2 h. The aqueous phase was separated and neutralized with concentrated HCl. The water was evaporated in vacuo and the residue taken up in MeOH, filtered, and the filtrate concentrated to give 40 (3.6 g) which was used in the next step without further purification.

- 33 -

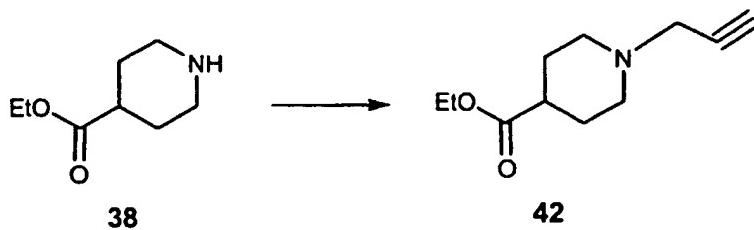
Step 3



In a manner similar to that described in Example 1, Step 2, compound 40 (0.2 g, 0.95 mmol) was converted to 41 (0.2 g, 47%). Mass spectrum : 448 ($M+H$).

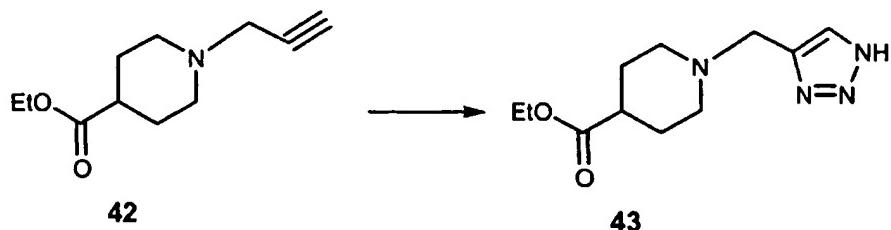
Example 8

Step 1



To a solution of 38 (2.57 g, 16 mmol) in THF (30 mL) was added propargyl bromide (1.34 g, 8.98 mmol) and the reaction heated to reflux overnight. After cooling to room temperature, the reaction was diluted with CH_2Cl_2 and washed with 1 N NaOH. The organic layer was dried and concentrated to give a residue which was purified by flash column chromatography (5% ethyl acetate in hexane) to give 42 (1.31 g, 75%). Mass spectrum: 196 ($M+H$).

Step 2

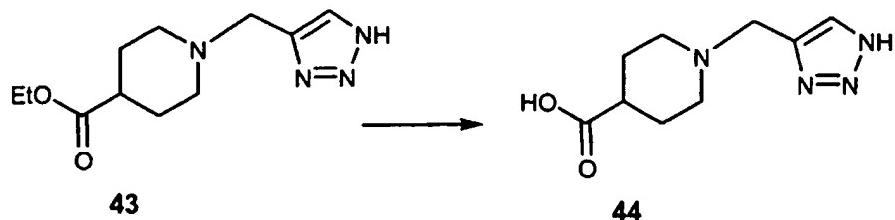


To a solution of 42 (0.5 g, 2.56 mmol) in toluene (10 mL) was added trimethylsilyl azide (0.62 g, 5.12 mmol) and the reaction was heated to reflux for 18 h. The reaction was cooled to room temperature, additional trimethylsilyl azide was added (0.7 mL). The reaction was stirred at 50° C for 8 days and 110° C for 10 days. The solvent was evaporated in vacuo, MeOH (100 mL) was added, and the MeOH

- 34 -

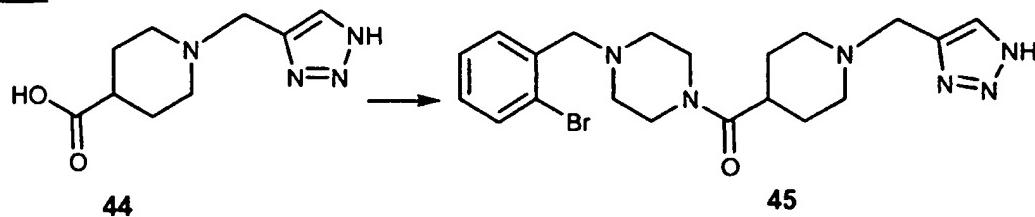
removed in vacuo. The residue so obtained was chromatographed (4% MeOH in ethyl acetate) to give **43** (0.5 g, 82%) Mass spectrum: 239 (M+H).

Step 3



In a manner similar to that described in Example 2, Step 4, Compound **43** (0.5 g, 2.1 mmol) was converted to compound **44** (0.44 g, 100%).

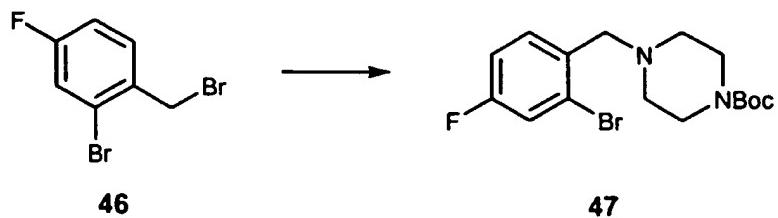
Step 4



In a manner similar to that described in Example 1, Step 2, **44** (0.25 g, 1.2 mmol) and **21** (0.36, 1.4 mmol) were converted to **45** (0.11 g, 20%). Mass spectrum: 447 (M+H).

Example 9

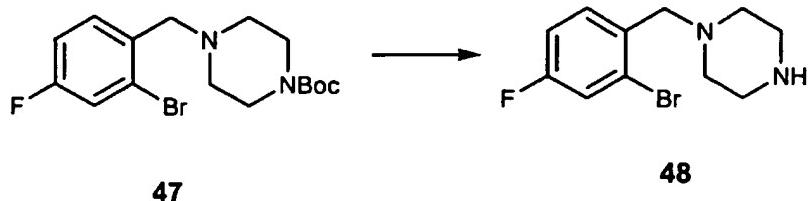
Step 1



A solution of compound **46** (2 g, 7.5 mmol), **19** (1.6 g, 8.2 mmol) and triethylamine (3.1 mL) in toluene (30 mL) was heated to reflux overnight. The solvent was evaporated and the residue partitioned between ethyl acetate and saturated NaHCO₃. The organic layer was dried and concentrated and the residue purified by flash column chromatography (30% ethyl acetate in hexane) to give **47** (1.6 g, 78%).

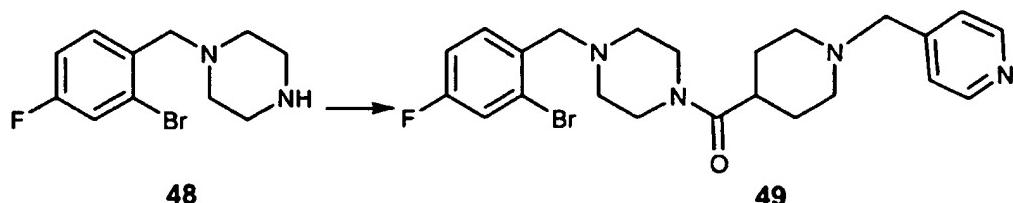
- 35 -

Step 2



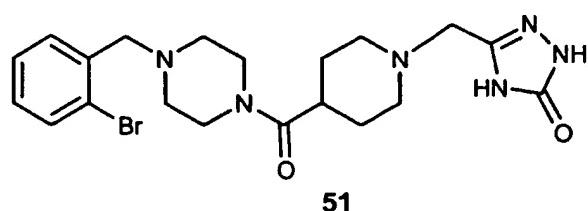
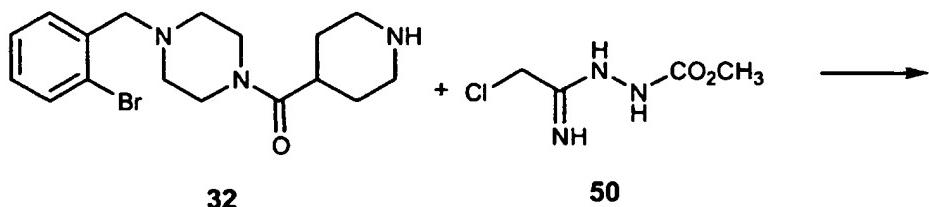
In a manner similar to that described in Example 1, Step 3, **47** (1.6 g, 4.3 mmol) was converted to **48** (1.5 g, 100%).

Step 3



In a manner similar to that described in Example 1, Step 2, **48** (0.38 g, 1.1 mmol) was converted to **49** (0.15 g, 35%). Mass spectrum: 475 (M+H).

Example 10

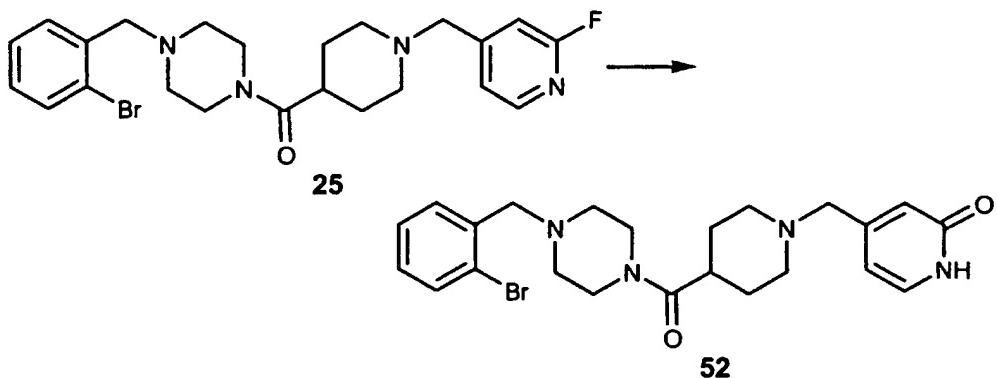


To a suspension of **32** (0.5 g, 1.14 mmol) in acetonitrile (5 mL) was added diisopropylethylamine (0.59 g, 4.56 mmol) followed after 10 min by **50** (0.23 g, 1.37 mmol). The mixture was stirred at room temperature for 48 h. The acetonitrile was removed, xylene (10 mL) was added and the reaction refluxed overnight. The reaction was cooled, diluted with ethyl acetate and washed with water. The organic

- 36 -

layer was dried and concentrated and chromatographed (10% to 20% MeOH in ethyl acetate) to give 51 (0.13 g, 25%). Mass spectrum: 463 ($M+H$).

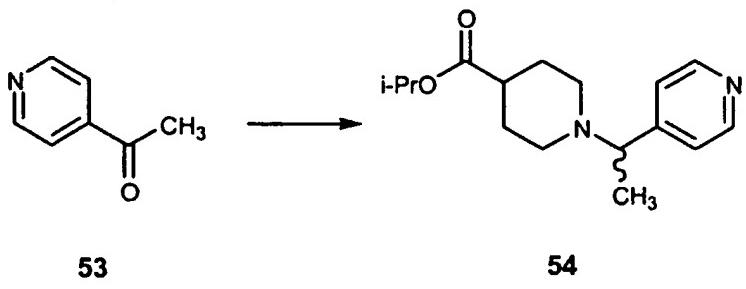
Example 11



A solution of **25** (0.13 g, 0.27 mmol) in 1:1 5% HCl in DME/water (4 mL) was heated to 60° C for 6 h. The reaction was cooled to room temperature, saturated NaHCO₃ and solid NaCl was added and the mixture was extracted with CH₂Cl₂. The combined organic layers were dried, concentrated and the residue purified by flash column chromatography (5-10% NH₃/MeOH in CH₂Cl₂) to give **52** (40 mg, 31%). Mass spectrum: 473 (M⁺).

Example 12

Step 1

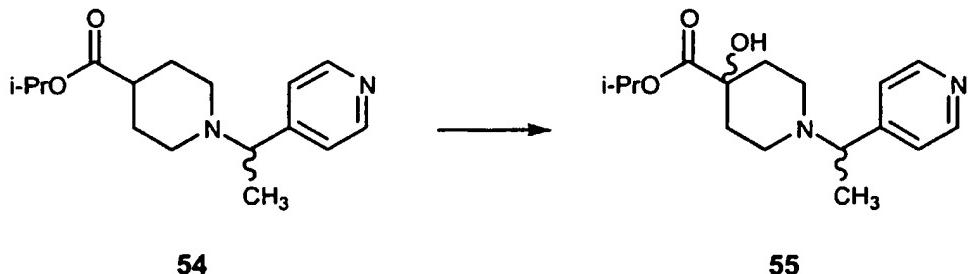


Compound **53** (3.6 g, 29.1 mmol), ethyl isonipecotate (5.8 g, 36.4 mmol) and Ti(O*i*Pr)₄ (10.3 g, 36.4 mmol) were combined and stirred at room temperature overnight. CH₂Cl₂ (100 mL) was added followed by NaBH(OAc)₃ (8.6 g, 40.8 mmol) and the reaction stirred overnight. Saturated NaHCO₃ was added and the mixture filtered through Celite. The filter cake was washed with additional CH₂Cl₂, and the

- 37 -

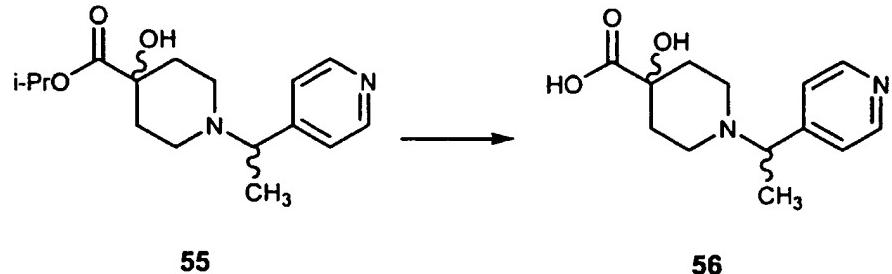
combined filtrates were washed with saturated NaHCO₃ and dried. Concentration gave a residue which was purified by flash column chromatography (8% MeOH in ethyl acetate) to give **54** (5 g, 83%). Mass spectrum: 277 (M+H).

Step 2

**54****55**

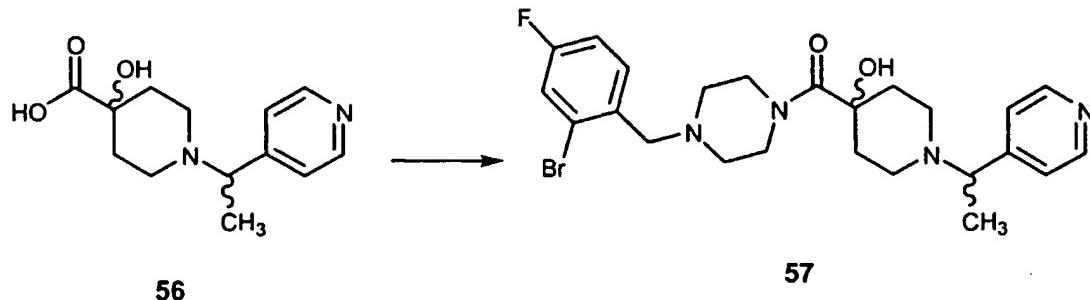
In a manner similar to that described in Example 4, Step 2, **54** (1 g, 3.6 mmol) was converted to **55** (0.4 g, 37%). Mass spectrum: 293 (M+H).

Step 3

**55****56**

In a manner similar to that described in Example 2, Step 4, **55** (0.4 g, 1.4 mmol) was converted to **56** (0.4 g, 100%).

Step 4

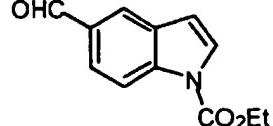
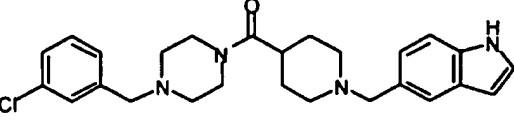
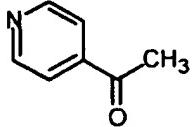
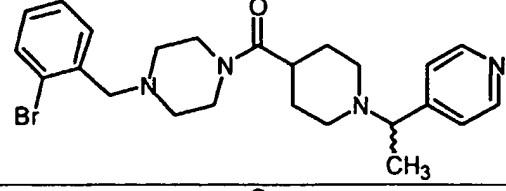
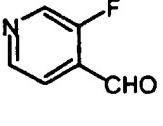
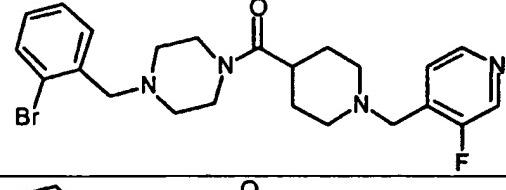
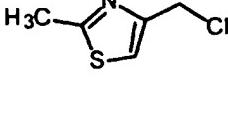
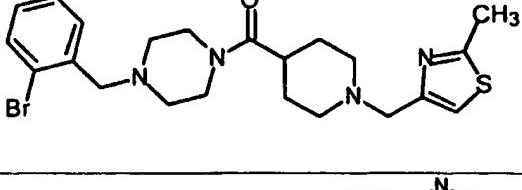
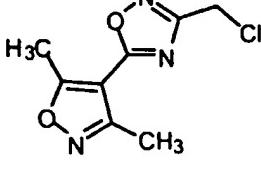
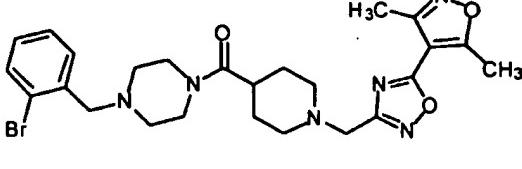
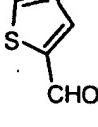
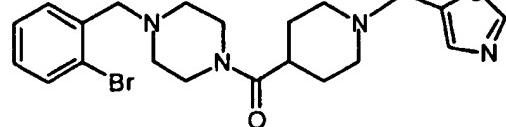
**56****57**

- 38 -

In a manner similar to that described in Example 1, Step 2, **56** (0.38 g, 1.6 mmol) was converted to **57** (0.36 g, 47%). Mass spectrum: 505 (M+H).

Using the procedures described in Examples 1 - 12, the compounds in Table 1 were synthesized:

TABLE 1

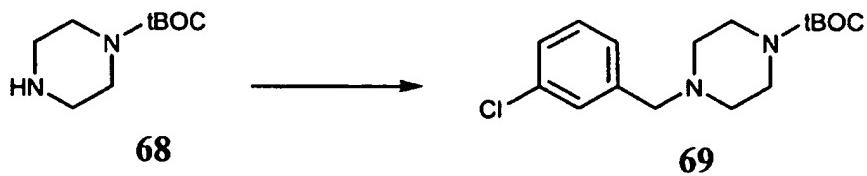
Compound Number	Starting Material	Product
58		
59		
60		
61		
62		
63		

- 39 -

64		
65		
52		
53		

Example 13

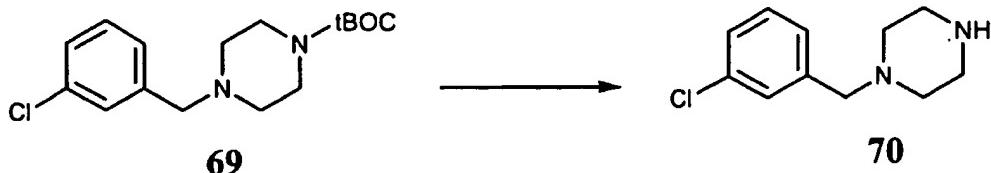
Step 1



Dissolved amine **68** (25.0 g, 0.134 mol) in CH_2Cl_2 (500 mL) and added 3 A sieves (25 g), 3-chlorobenzaldehyde (28.3 g, 0.201 mol), and sodium triacetoxyborohydride (42.6 g, 0.201 mol). Stirred at 23° C for 16 h and filtered. Washed filtrate with saturated NaHCO_3 then saturated NaCl . Dried organic extract (MgSO_4), filtered, and concentrated. Purified by silica gel chromatography (eluant: 20% EtOAc-hexane) to give 31.0 g (0.100 mol, 74%) of the product **69** as a yellow oil. MS (ES for M+1): m/e 312.

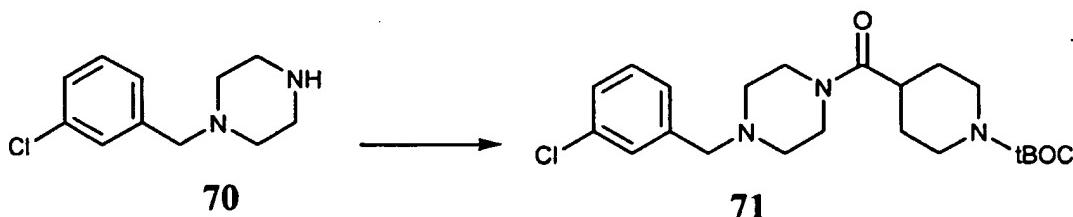
- 40 -

Step 2



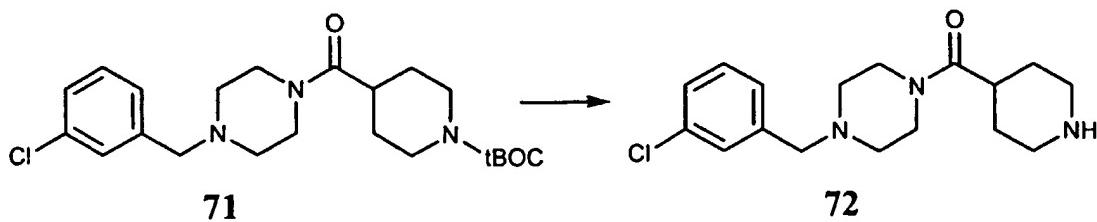
Dissolved compound **69** (27.0 g, 0.087 mol) in CH₂Cl₂ (500 mL) and added 1.0 N HCl in ether (275 mL, 0.275 mol). Stirred at 23° C for 96 h. Filtered and washed with ether to give 20.0 g of the dihydrochloride salt of compound **70**. Dissolved the dihydrochloride salt in 1 N NaOH (500 mL) and extracted with EtOAc. Dried combined organic extracts (MgSO₄), filtered, and concentrated to give 14.9 g (0.071 mol, 82%) of the product **70** as a yellow oil. MS (ES for M+1): m/e 211.

Step 3



Combined compound **70** (13.03 g, 0.062 mol), N-tBOC-isonipecotic acid (21.38 g, 0.093 mol), HOBT (16.28 g, 0.12 mol), and DEC (23.01 g, 0.12 mol) in CH_2Cl_2 (400 mL). Stirred at 23° C for 4 h. Added 2 N NaOH and extracted with CH_2Cl_2 . Dried combined organic extracts (MgSO_4), filtered, and concentrated. Purified by silica gel chromatography (eluant: CH_2Cl_2 then 2% MeOH with $\text{NH}_3\text{-CH}_2\text{Cl}_2$) to give 25.0 g (0.059 mol, 95%) of the product **71** as a yellow oil. MS (ES for M+1): m/e 422.

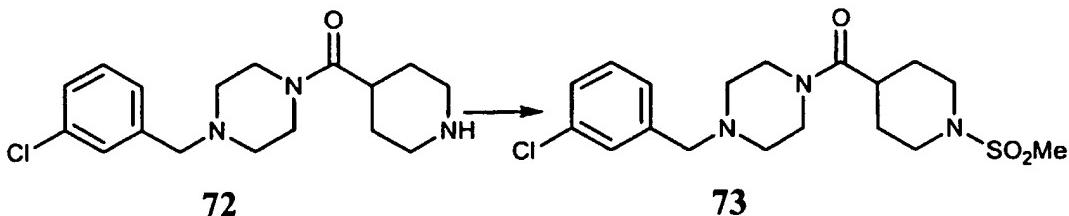
Step 4



- 41 -

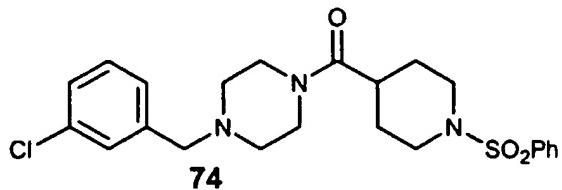
Dissolved compound **71** (20.0 g, 0.048 mol) in CH₂Cl₂ (250 mL) and cooled to 0° C. Added TFA (50 mL) and stirred at 23° C for 3 h. Concentrated, added 6.25 N NaOH, and extracted with CH₂Cl₂. Dried combined organic extracts (MgSO₄), filtered, and concentrated. Purified by silica gel chromatography (eluant: CH₂Cl₂ then 5% MeOH with NH₃-CH₂Cl₂) to give 7.18 g (0.022 mol, 47%) of the product **72** as a yellow oil. MS (ES for M+1): m/e 322.

Step 5



Dissolved compound **72** (255 mg, 0.79 mmol) in CH₂Cl₂ (10 mL) and cooled to 0° C. Added triethylamine (158 mg, 0.22 mL, 1.56 mmol) and mesyl chloride (115 mg, 0.078 mL, 1.01 mmol). Warmed to 23° C and stirred for 16 h. Added saturated NaHCO₃ and extracted with CH₂Cl₂. Dried combined organic extracts (MgSO₄), filtered, and concentrated. Purified by silica gel chromatography (eluant: CH₂Cl₂ then 2% MeOH with NH₃-CH₂Cl₂) to give 164 mg (0.41 mmol, 52%) of the product **73** as a white foam. MS (ES for M+1): m/e 400.

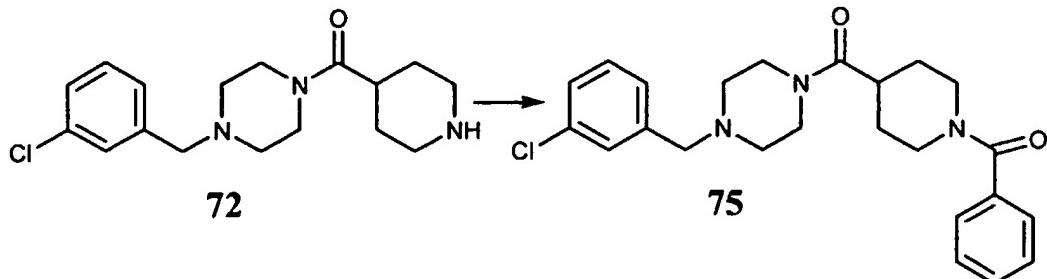
Following the above procedure compound **74** was prepared:



(MS(ES) 462 (M+1)).

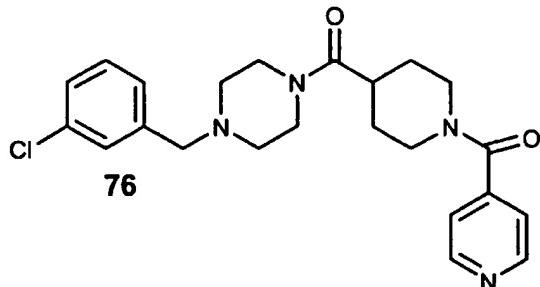
- 42 -

Example 14



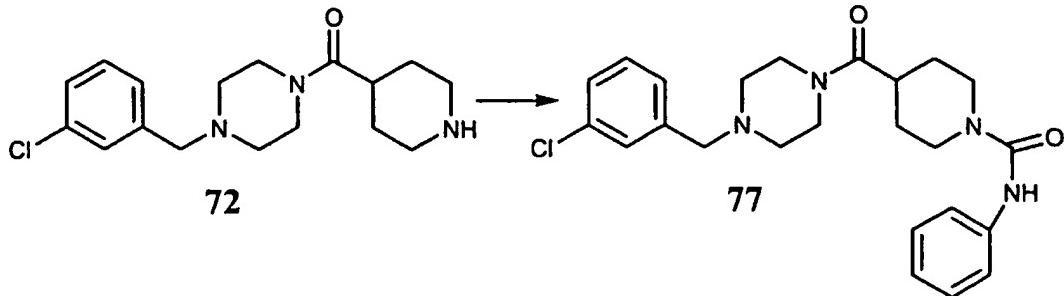
Dissolved compound **72** (250 mg, 0.78 mmol) and triethylamine (158 mg, 0.22 mL, 1.56 mmol) in CH_2Cl_2 (10 mL) and cooled to 0° C. Added benzoyl chloride (142 mg, 0.12 mL, 1.01 mmol). Warmed to 23° C and stirred for 16 h. Added saturated NaHCO_3 and extracted with CH_2Cl_2 . Dried combined organic extracts (MgSO_4), filtered, and concentrated. Purified by silica gel chromatography (eluant: CH_2Cl_2 then 3% MeOH with $\text{NH}_3\text{-CH}_2\text{Cl}_2$) to give 191 mg (0.45 mmol, 58%) of the product **75** as a white foam. MS (ES for M+1): m/e 426.

Following the above procedure compound 76 was prepared:



(MS(ES) 427 (M+1)).

Example 15

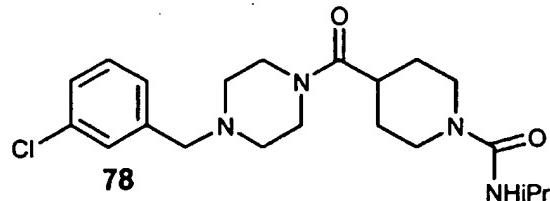


Dissolved compound **72** (250 mg, 0.78 mmol) and triethylamine (158 mg, 0.22 mL, 1.56 mmol) in dry THF (10 mL). Added phenylisocyanate (120 mg, 0.11 mL, 1.0

- 43 -

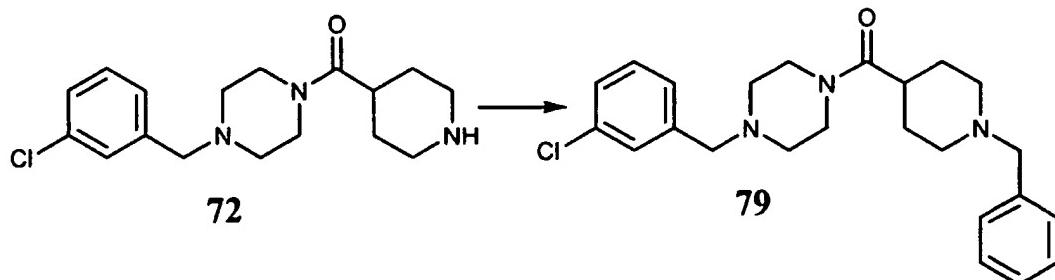
mmol) and stirred at 23° C for 16 h. Added water and extracted with EtOAc. Dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: CH_2Cl_2 then 3% MeOH with $NH_3\text{-}CH_2Cl_2$) to give 170 mg (0.39 mmol, 50%) of the product **77** as a white foam. MS (ES for $M+1$): m/e 441.

Following the above procedure compound **78** was prepared:



(MS(ES) 407 ($M+1$)).

Example 16



Combined compound **72** (550 mg, 1.71 mmol), benzaldehyde (109 mg, 1.03 mmol), 0.5 g of crushed 3A sieves, and sodium triacetoxyborohydride (347 mg, 1.64 mmol) in 2:1 $CH_2Cl_2\text{:EtOH}$ (15 mL). Stirred at 23° C for 16 h. Added saturated $NaHCO_3$ and extracted with CH_2Cl_2 . Dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: CH_2Cl_2 then 3% MeOH with $NH_3\text{-}CH_2Cl_2$) to give 260 mg (0.63 mmol, 37%) of the product **79** as a white foam. MS (ES for $M+1$): m/e 412.

Following the above procedure the compounds in Table 2 were prepared.

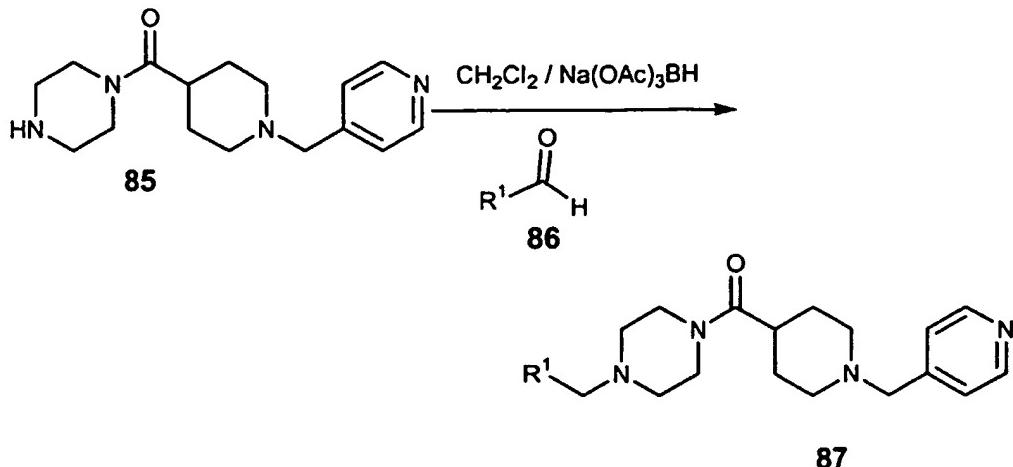
- 44 -

TABLE 2

Compound Number	Compound	MS (ES)
80		442 (M+1)
81		469 (M+1)
82		413 (M+1)
83		413 (M+1)
84		429 (M+1)

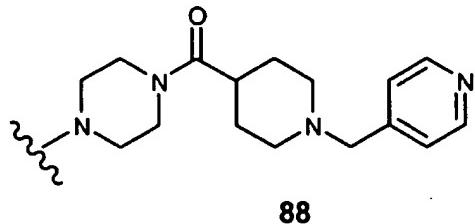
- 45 -

Example 17: General procedure for reductive amination, parallel synthesis.



A solution of the amine **85** (0.063 mmol) and the aldehyde **86** (0.32 mmol, 1.0 M in dichloroethane) is treated with NaBH(OAc)_3 (0.32 mmol, 0.5 M in dichloroethane) and placed on shaker for an average period of 18 h. Where needed more NaBH(OAc)_3 is added to force the reaction into completion. Amberlyst-15 resin (~100 mg) is added and the reaction mixture shaken for an additional hour while monitoring by TLC (10% NH_3 saturated methanol in CH_2Cl_2 , $R_f \sim 0.3$) to ensure no amine product remained in solution. The resin is filtered and alternately washed six times with MeOH and dichloroethane. The resin is extracted by stirring twice, for 30 min, with 2N NH_3/MeOH (2 ml) and rinsing twice with MeOH (2 ml). The combined extracts are concentrated in vacuo to provide the desired product **65**.

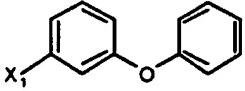
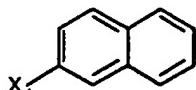
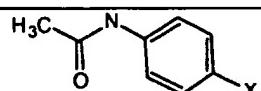
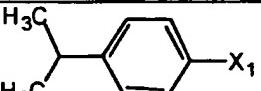
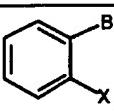
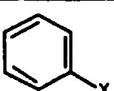
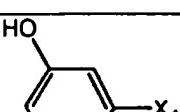
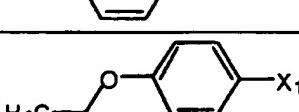
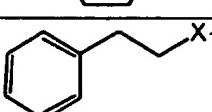
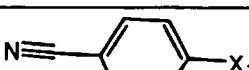
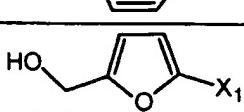
Using this procedure, the compounds listed in **Table 3** were synthesized. In **Table 3** X_1 represents the moiety:



(i.e., the moiety **88** is compound **87** without the R^1CH_2 -group).

- 46 -

TABLE 3

Compound No.	R¹	MS
89		471.1 (MH ⁺)
90		429.1 (MH ⁺)
91		436.1 (MH ⁺)
92		421.1 (MH ⁺)
93		459.1581 (MH ⁺)
94		379.1 (MH ⁺)
95		395.1 (MH ⁺)
96		423.1 (MH ⁺)
97		413.1 (MH ⁺)
98		407.1 (MH ⁺)
99		404.1 (MH ⁺)
100		399.1 (MH ⁺)

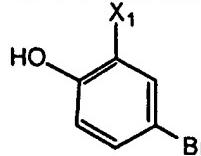
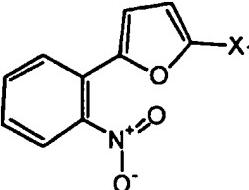
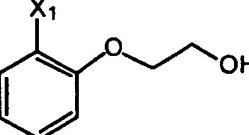
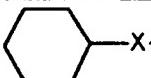
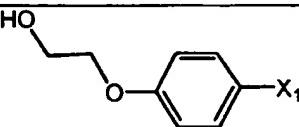
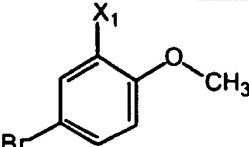
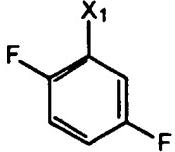
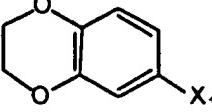
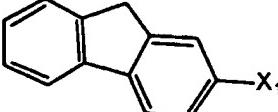
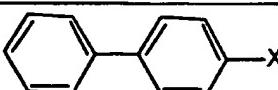
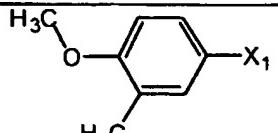
- 47 -

101		521.1 (M^+)
102		423.1 (MH^+)
103		439.1 (MH^+)
104		393.1 (MH^+)
105		409.1 (MH^+)
106		490.1 (MH^+)
107		409.1 (MH^+)
108		409.1 (MH^+)

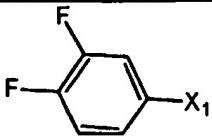
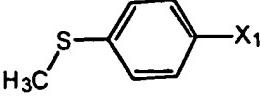
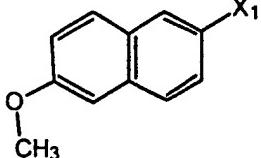
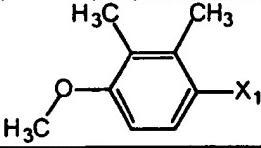
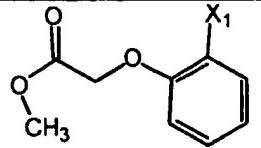
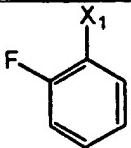
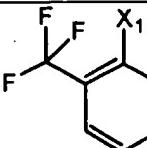
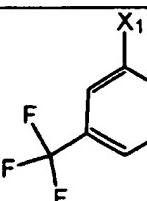
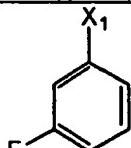
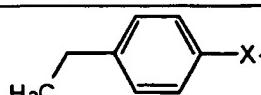
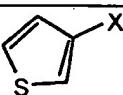
- 48 -

109		437.1 (MH ⁺)
110		407.1 (MH ⁺)
111		459.1 (MH ⁺)
112		421.1 (MH ⁺)
113		553.1 (M ⁺)
114		485.1 (MH ⁺)
115		537.1 (M ⁺)

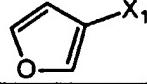
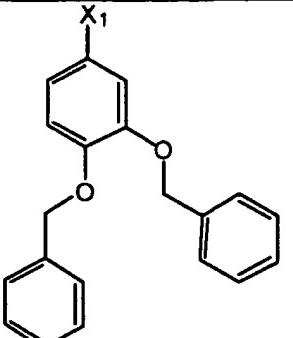
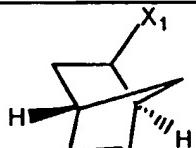
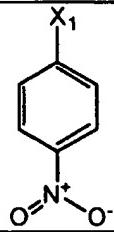
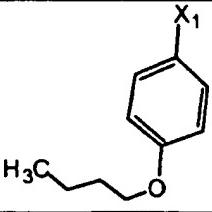
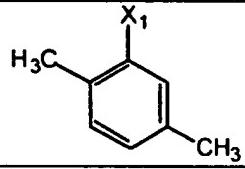
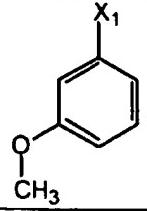
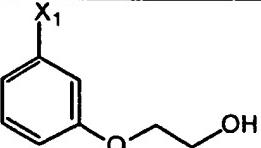
- 49 -

116		473.1 (M^+)
117		490.1 (MH^+)
118		439.1 (MH^+)
119		485.1 (MH^+)
120		439.1 (MH^+)
121		488.1 (MH^+)
122		415.1 (MH^+)
123		437.1 (MH^+)
124		467.1 (MH^+)
125		455.1 (MH^+)
126		423.1 (MH^+)

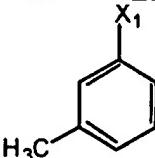
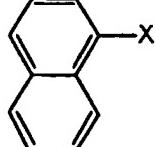
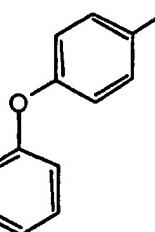
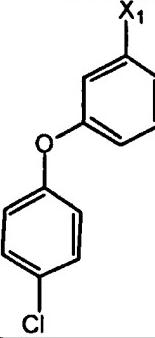
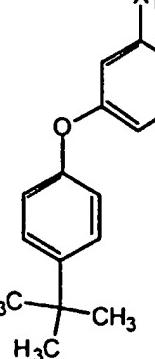
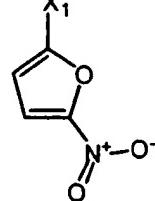
- 50 -

127		415.1 (MH ⁺)
128		425.1 (MH ⁺)
129		459.1 (MH ⁺)
130		437.1 (MH ⁺)
131		467.1 (MH ⁺)
132		397.1 (MH ⁺)
133		447.1 (MH ⁺)
134		447.1 (MH ⁺)
135		397.1 (MH ⁺)
136		407.1 (MH ⁺)
137		385.1 (MH ⁺)

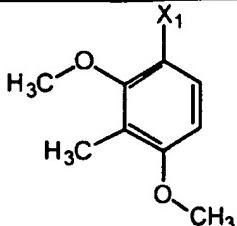
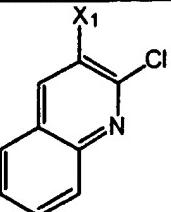
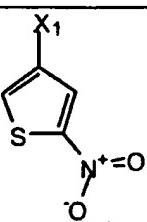
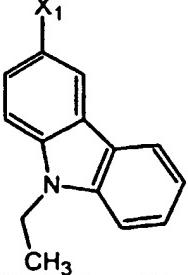
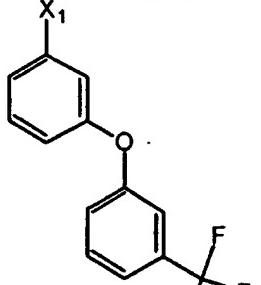
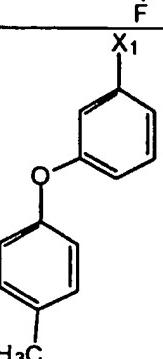
- 51 -

138		369.1 (MH ⁺)
139		591.1 (MH ⁺)
140		395.1 (MH ⁺)
141		424.1 (MH ⁺)
142		451.1 (MH ⁺)
143		407.1 (MH ⁺)
144		409.1 (MH ⁺)
145		439.1 (MH ⁺)

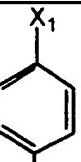
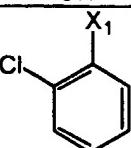
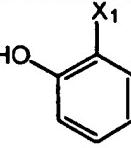
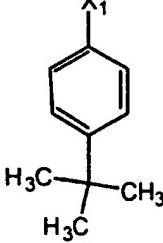
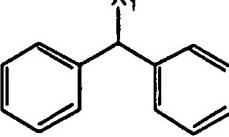
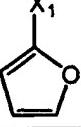
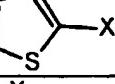
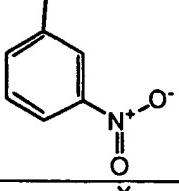
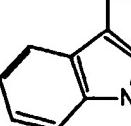
- 52 -

146		393.1 (MH ⁺)
147		429.1 (MH ⁺)
148		471.1 (MH ⁺)
149		505.1 (M ⁺)
150		527.1 (MH ⁺)
151		414.1 (MH ⁺)

- 53 -

152		453.1 (MH^+)
153		464.1 (M^+)
154		430.1 (MH^+)
155		496.1 (MH^+)
156		539.1 (MH^+)
157		485.1 (MH^+)

- 54 -

159		395.1 (MH ⁺)
160		413.1 (MH ⁺)
161		395.1 (MH ⁺)
162		435.1 (MH ⁺)
163		469.1 (MH ⁺)
164		369.1 (MH ⁺)
165		385.1 (MH ⁺)
166		424.1 (MH ⁺)
167		418.1 (MH ⁺)

- 55 -

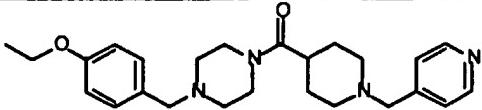
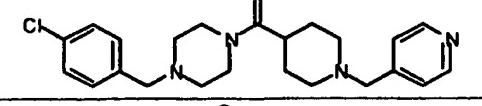
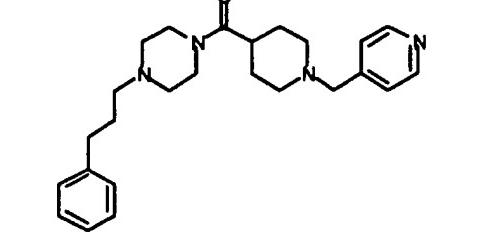
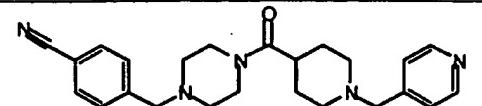
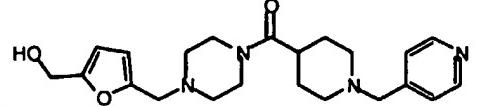
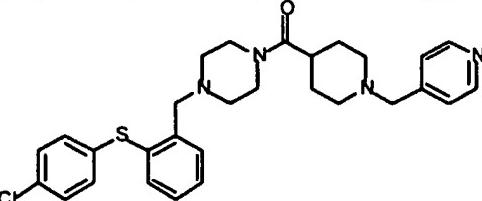
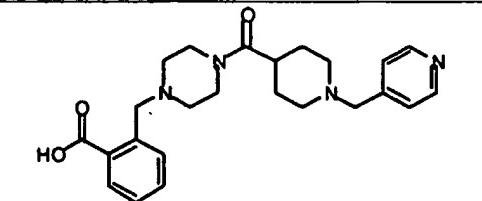
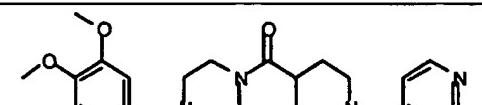
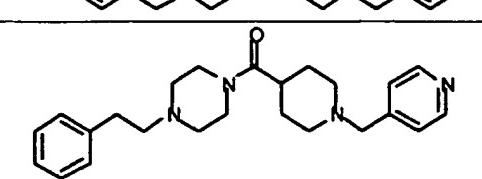
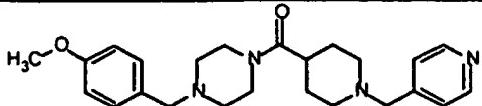
168		505 (MH ⁺)
-----	--	------------------------

Thus, compounds in Table 3 have the formulas given in Table 4 below.

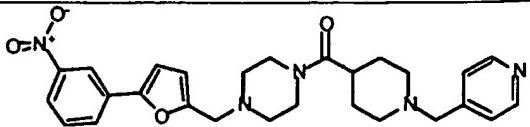
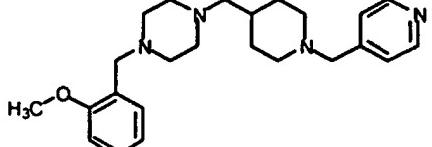
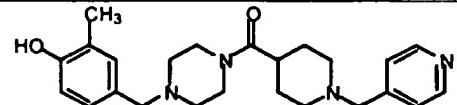
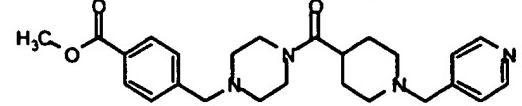
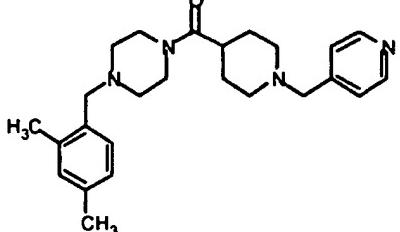
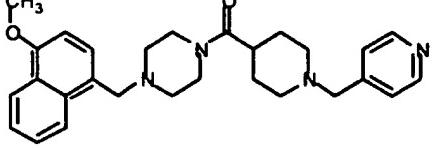
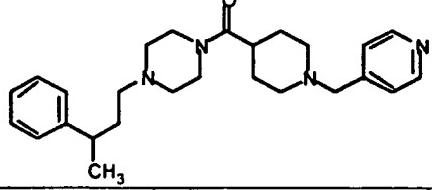
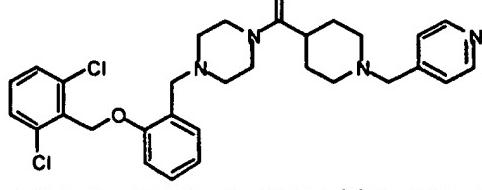
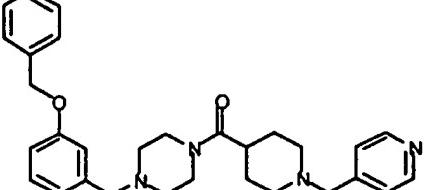
TABLE 4

Compound No.	Structure
89	
90	
91	
92	
93	
94	
95	

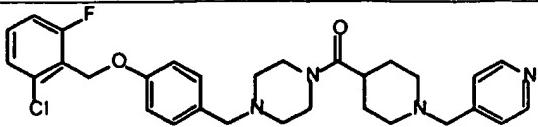
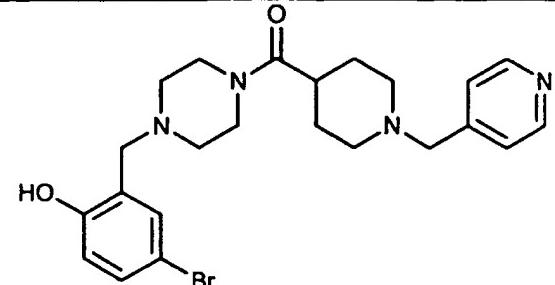
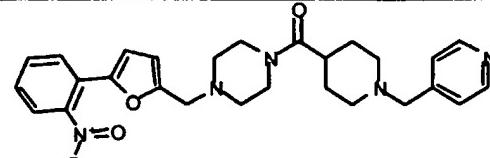
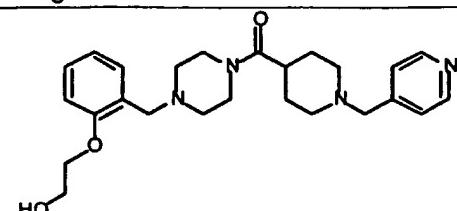
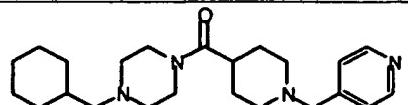
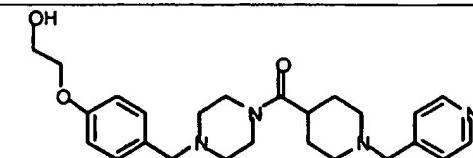
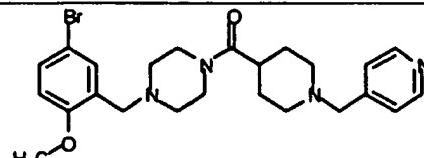
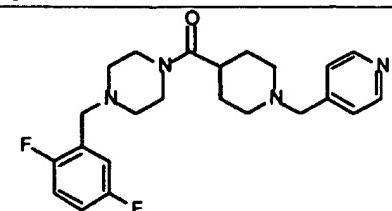
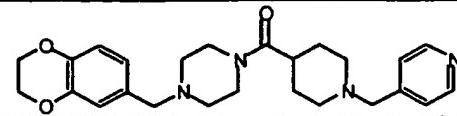
- 56 -

96	
97	
98	
99	
100	
101	
102	
103	
104	
105	

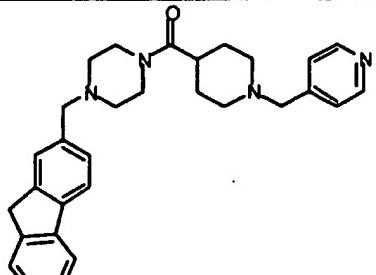
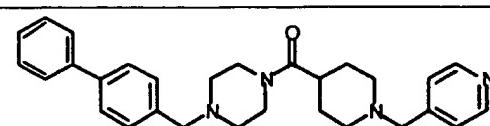
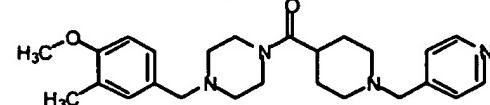
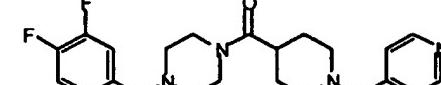
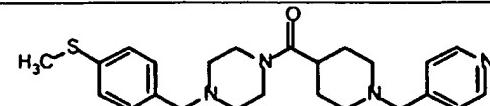
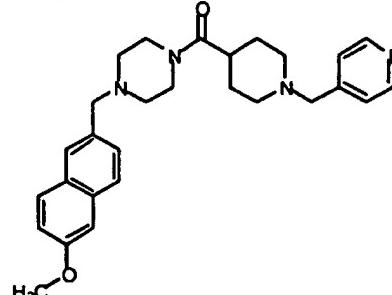
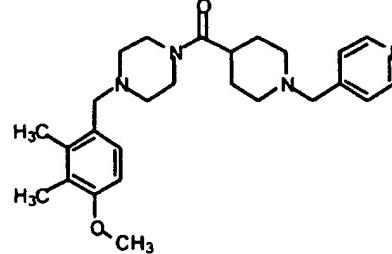
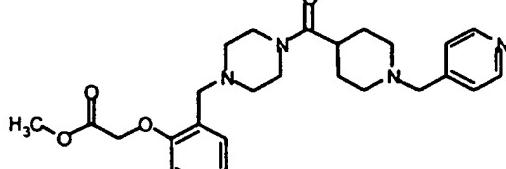
- 57 -

106	
107	
108	
109	
110	
111	
112	
113	
114	

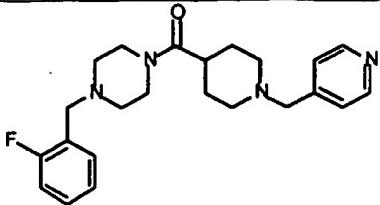
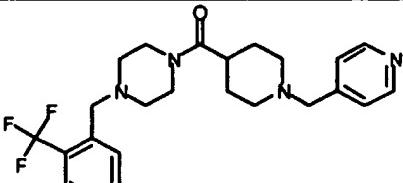
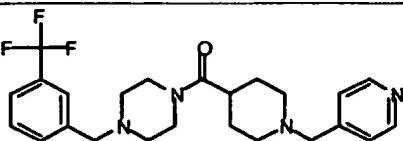
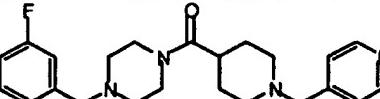
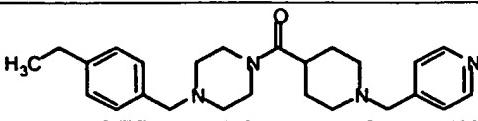
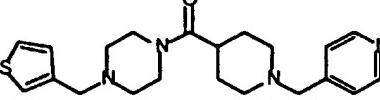
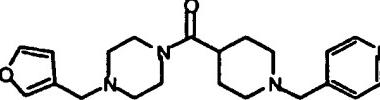
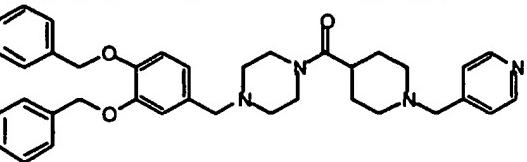
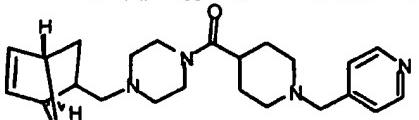
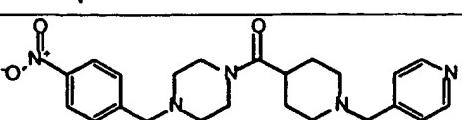
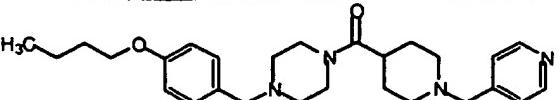
- 58 -

115	
116	
117	
118	
119	
120	
121	
122	
123	

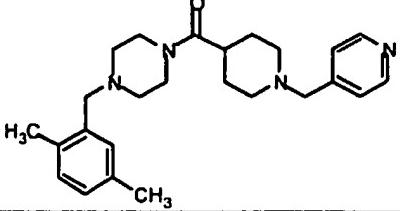
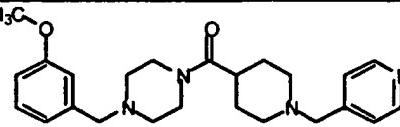
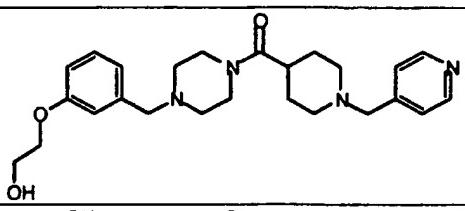
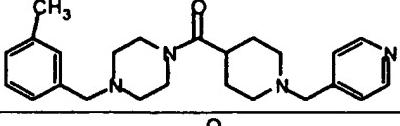
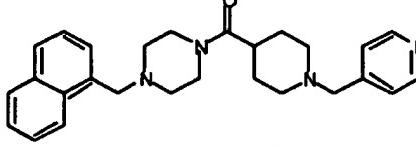
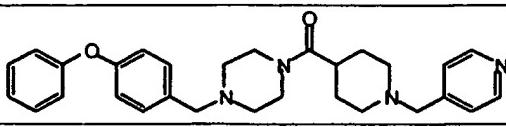
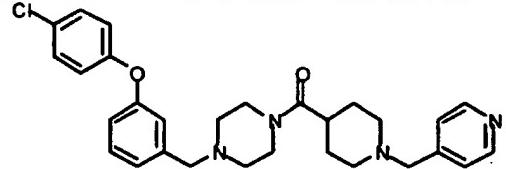
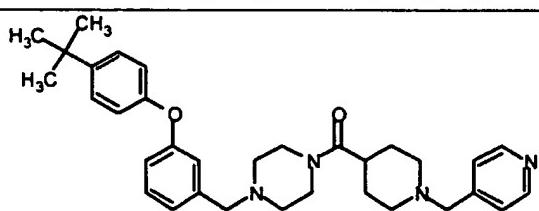
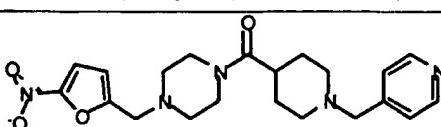
- 59 -

124	
125	
126	
127	
128	
129	
130	
131	

- 60 -

132	
133	
134	
135	
136	
137	
138	
139	
140	
141	
142	

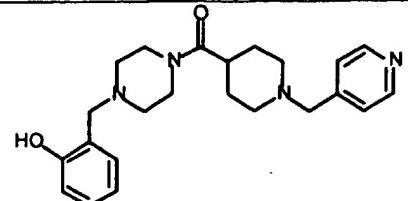
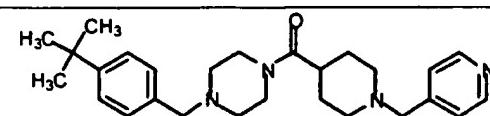
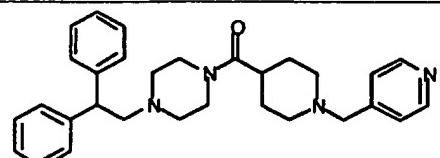
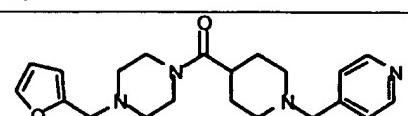
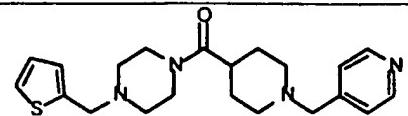
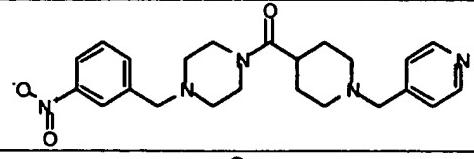
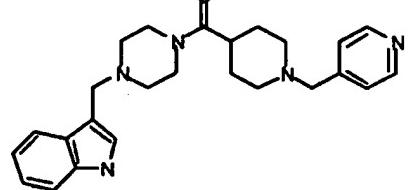
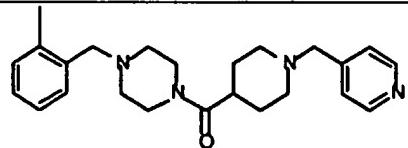
- 61 -

143	
142	
145	
146	
147	
148	
149	
150	
151	

- 62 -

152	
153	
154	
155	
156	
157	
159	
160	

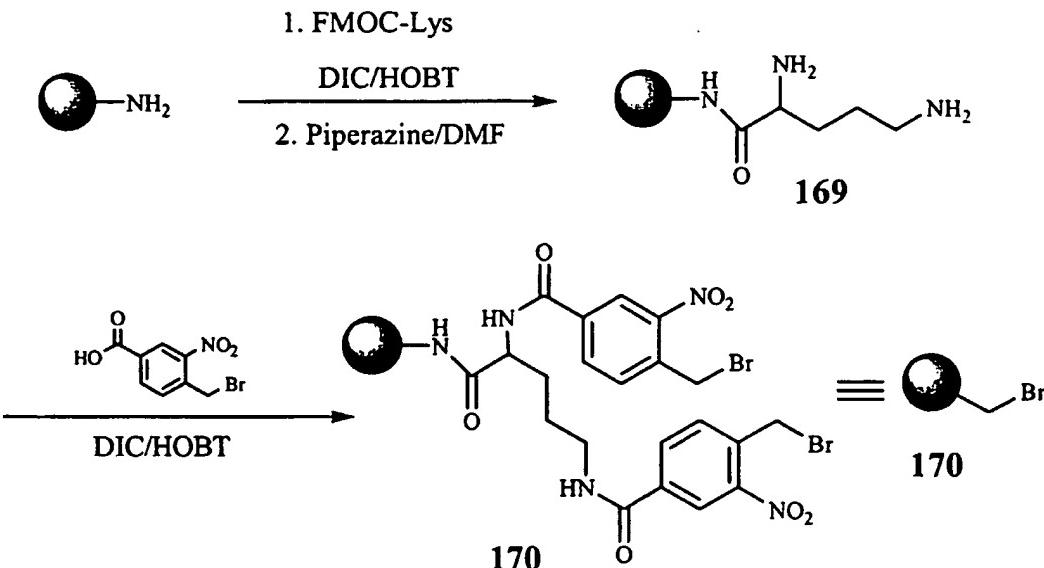
- 63 -

161	
162	
163	
164	
165	
166	
167	
168	

- 64 -

Example 18: Library preparation on solid phase

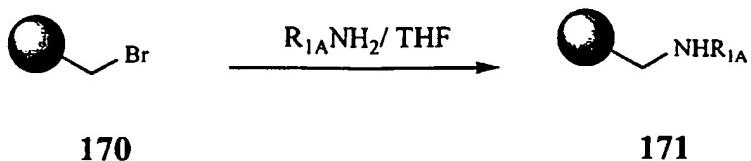
Schem. 1



TentaGel amino resin (1 eq.) was placed in a reaction vessel, dichloromethane, Fmoc-Lysine (2 eq.) and HOBT (2.2 eq.) were added followed by the addition of DIC (2eq.). The mixture was shaken at room temperature for 12 hours, then drained and the resin was washed with dichloromethane twice and DMF three times, and treated with 20% piperazine in DMF (v/v) for 30 minutes. The resin was then washed with DMF twice, methanol twice and dichloromethane three times, and dried overnight in vacuo to give amine resin 169.

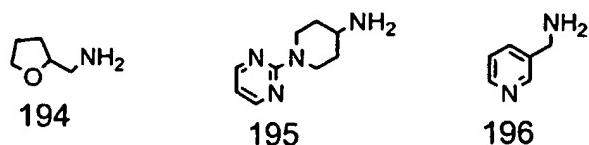
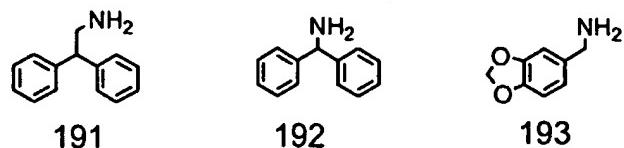
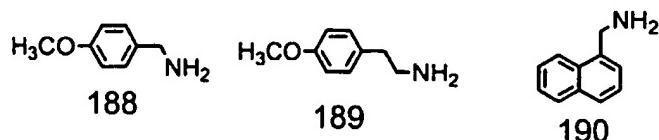
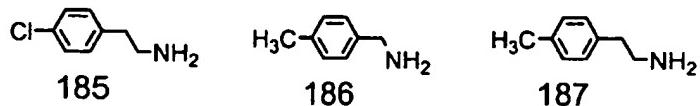
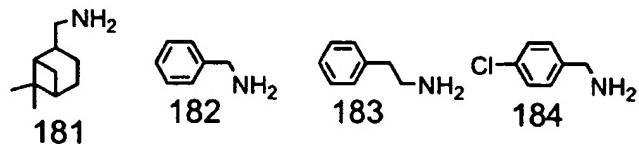
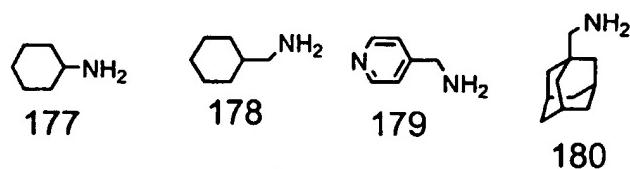
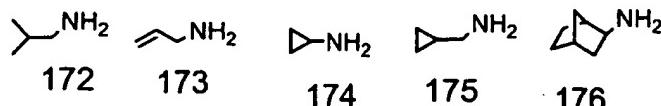
The amine resin **169** (1 eq.) was placed in a reaction vessel, dichloromethane, 4-bromomethyl-3-nitrobenzoic acid (2 eq.) and HOBT (2.2 eq.) were added followed by the addition of DIC (2eq.). The mixture was shaken at room temperature for 12 hours, then drained and the resin was washed with dichloromethane twice, methanol twice and dichloromethane three times, and dried overnight in *vacuo* to give bromoresin **170**.

Scheme 2



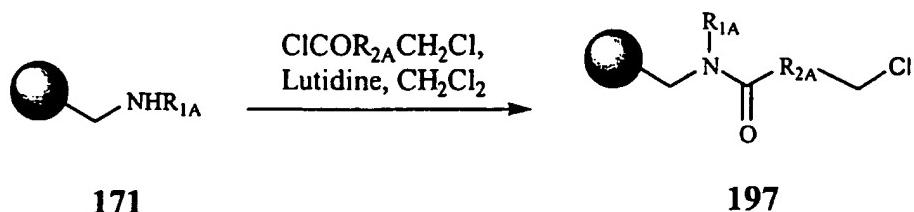
- 65 -

The bromo resin 170 was divided into 24 portions, and each (1eq.) was treated with an amine (see 172 to 196 below) (5eq.) in THF. The mixture was shaken at room temperature overnight, drained and the resin was washed with THF twice, DMF twice and dichloromethane three times, and dried overnight in *vacuo* to give amine resin 171.

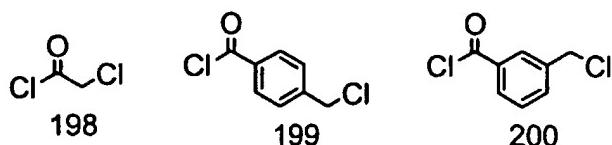


- 66 -

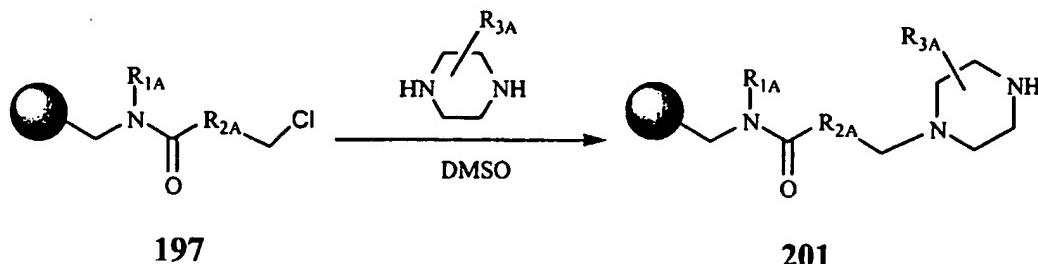
Scheme 3



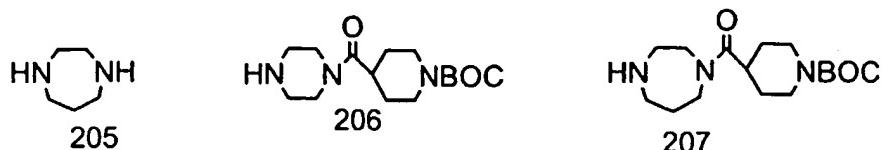
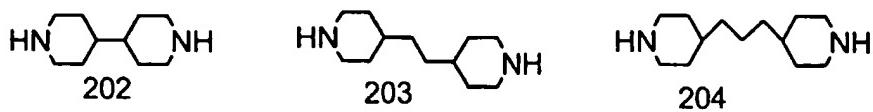
The amine resin **171** was divided into 3 portions, and each (1 eq.) was treated with an acid chloride (see **198** to **200** below)(2 eq.) and 2,6-lutidine (4 eq.) in dichloromethane. The mixture was shaken at room temperature for 30 minutes, drained and the resin was washed with dichloromethane twice, methanol twice and dichloromethane three times, and dried overnight in *vacuo* to give chlororesin **197**.



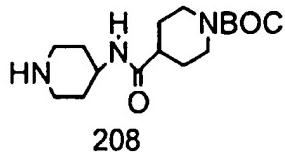
Scheme 4



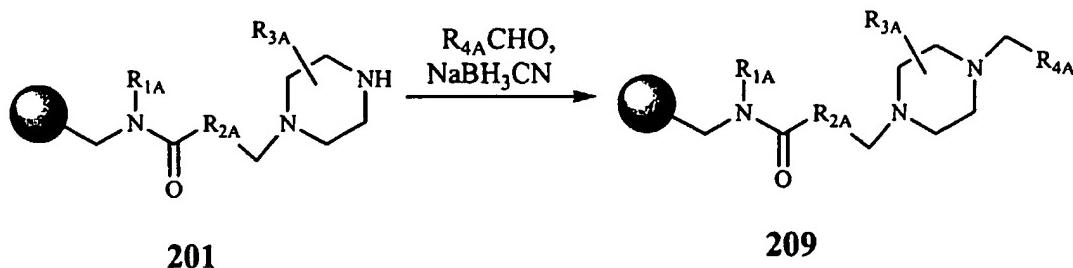
The chlororesin **197** was divided into 7 portions, and each (1 eq.) was treated with an appropriate amine (see **202** to **208** below) (5 eq.) in DMSO. The mixture was shaken at room temperature overnight, drained and the resin was washed with methanol twice, dichloromethane twice, methanol twice and dichloromethane three times, and dried in *vacuo* to give amine resin **201**.



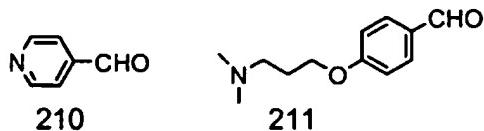
- 67 -



Scheme 5

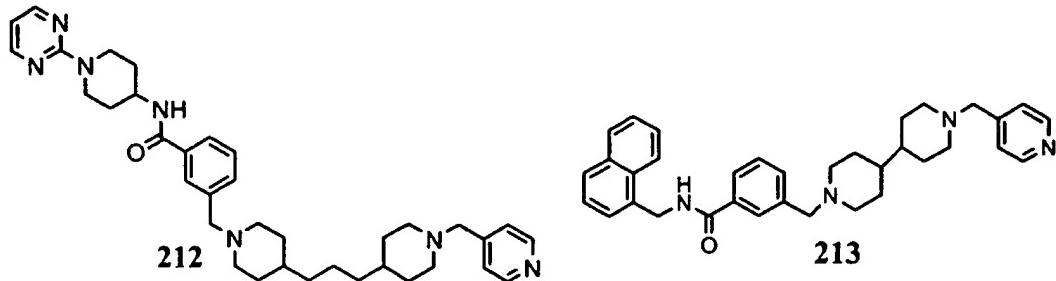


The amine resin **201** was divided into 2 reaction vessels, and each was treated with 2% HOAc in DMF and an appropriate aldehyde (see **210-211** below). The mixture was shaken at room temperature for 30 minutes, and NaBH₃CN was added to each reaction vessel. The mixture was shaken for overnight, drained, and the resin was washed with DMF twice, methanol three times and 10% HCl in methanol, and dried in *vacuo* to give resin **209**.

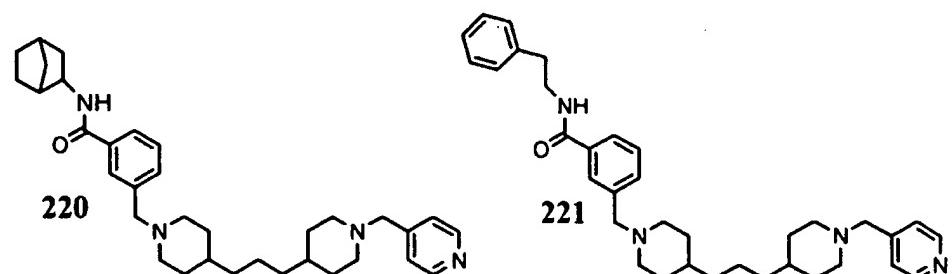
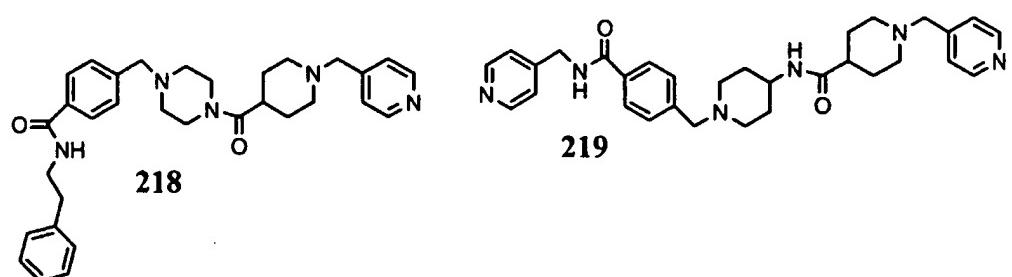
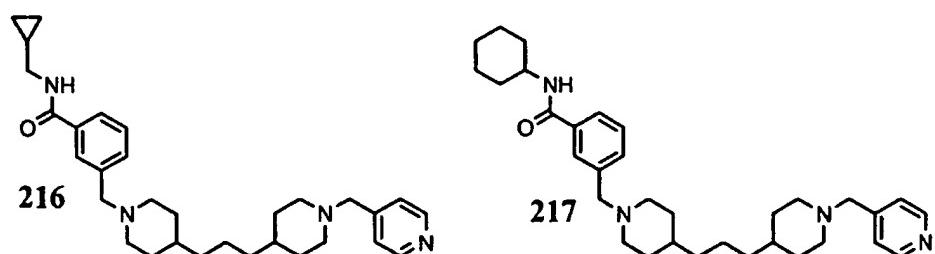
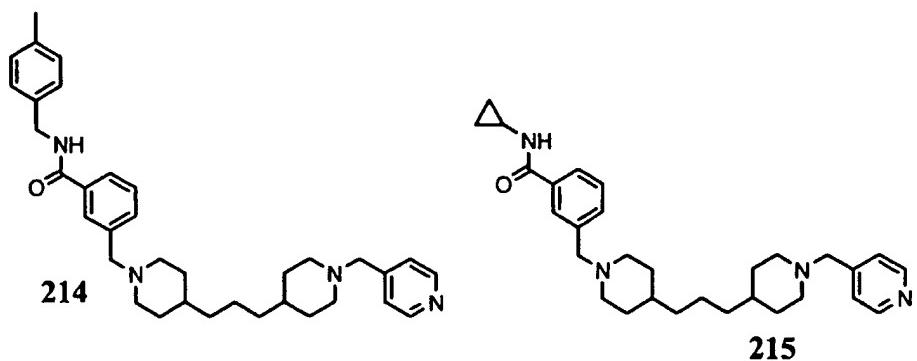


In the above Schemes, R_{1A} represents the substituents on R¹, R_{2A} represents R¹, R_{3A} represents R¹² or R¹³, and R_{4A} represents R².

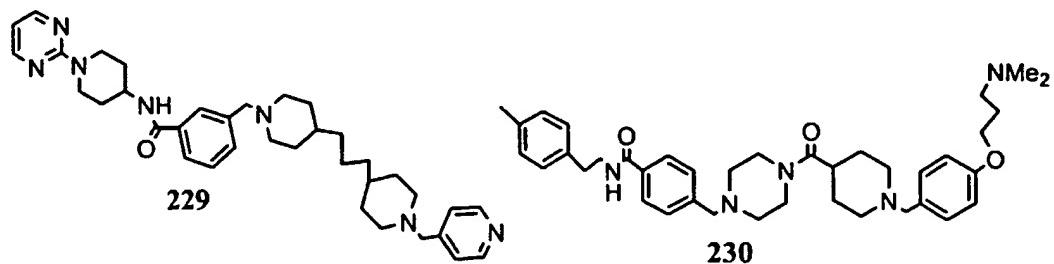
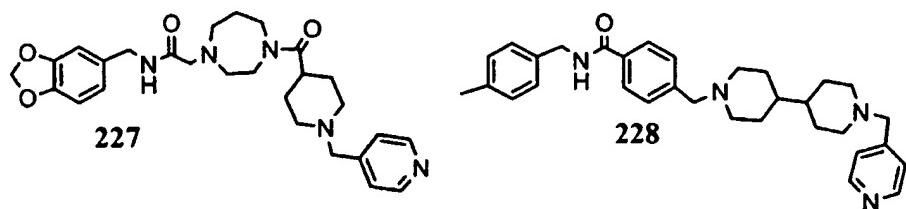
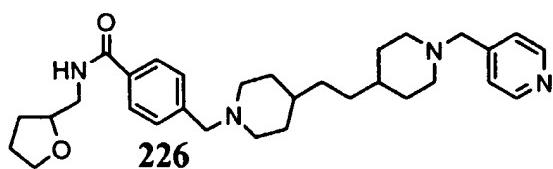
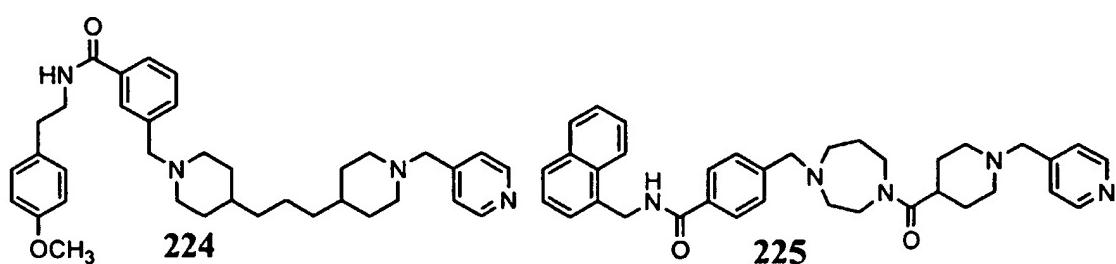
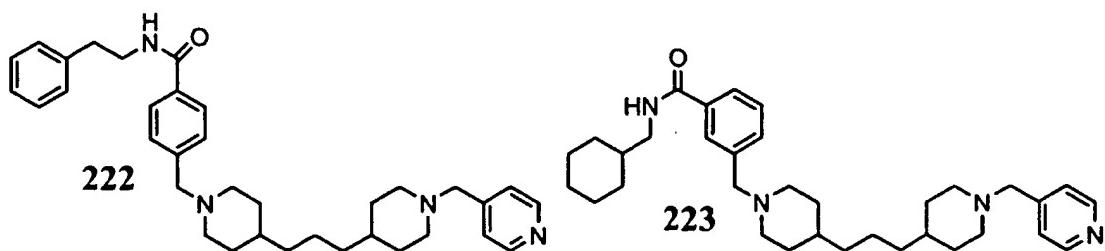
Examples of compounds made by the above library procedure include:



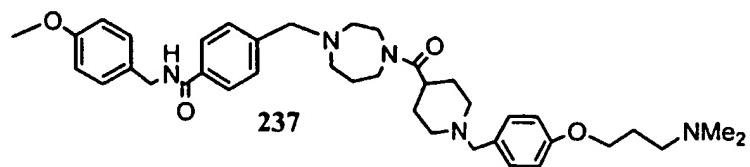
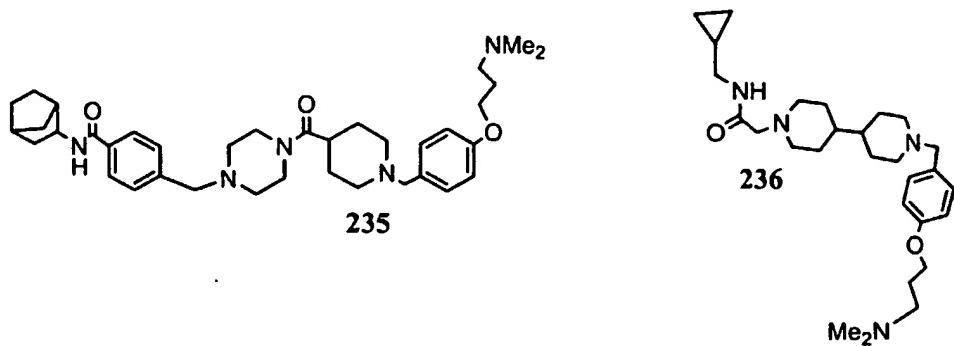
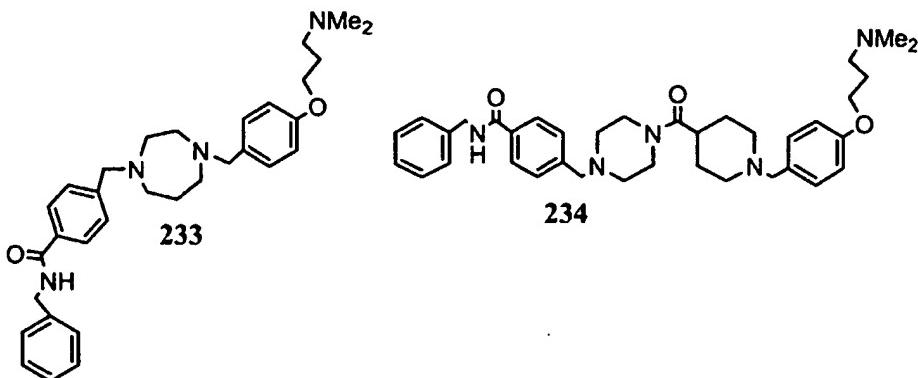
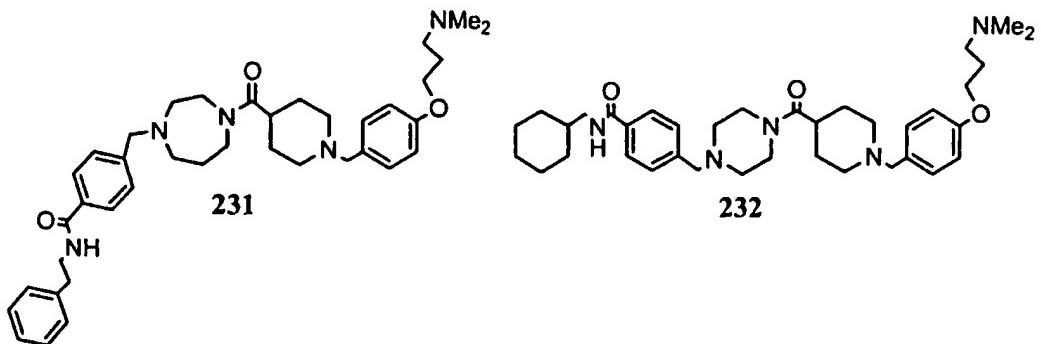
- 68 -



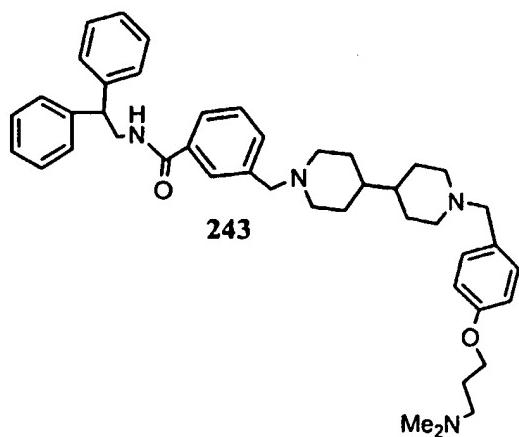
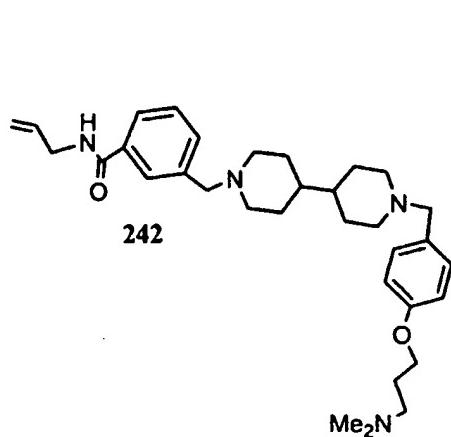
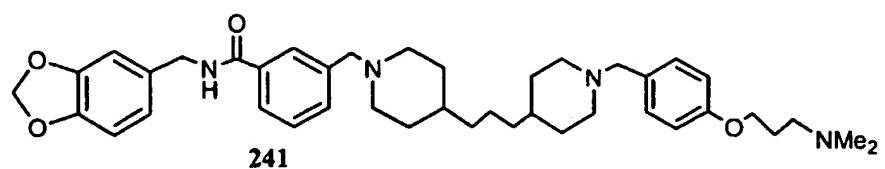
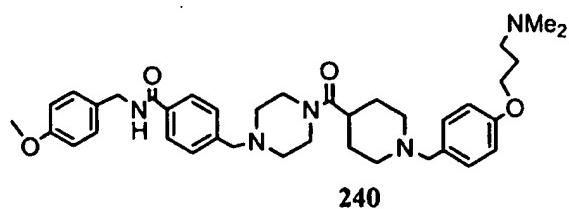
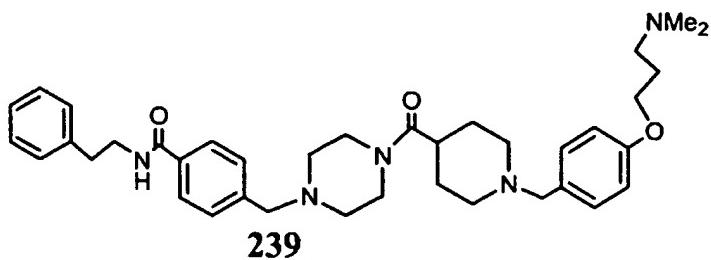
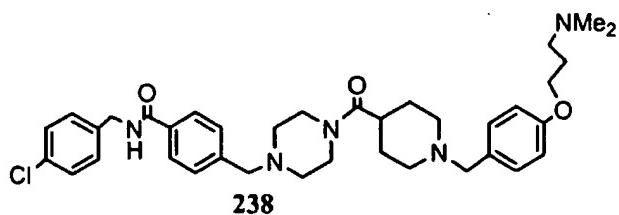
- 69 -



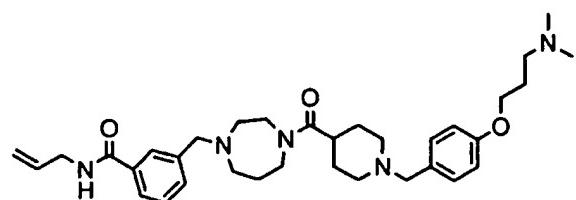
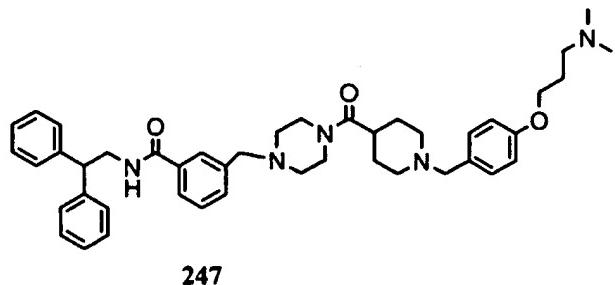
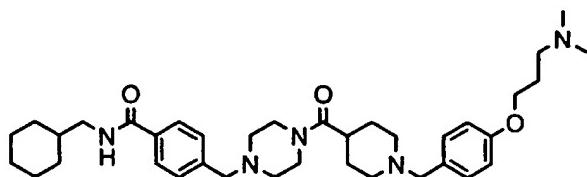
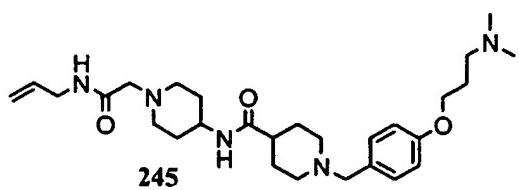
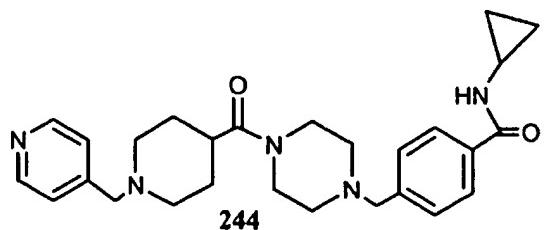
- 70 -



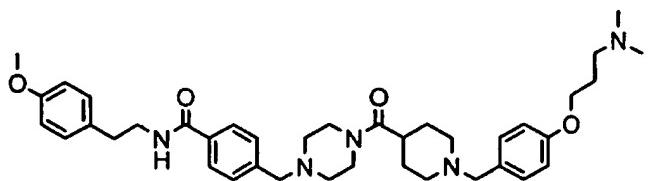
- 71 -



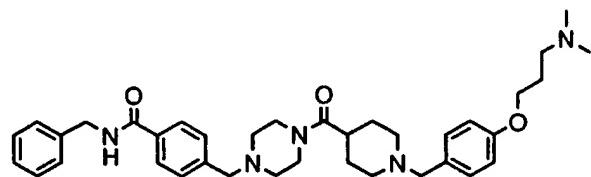
- 72 -



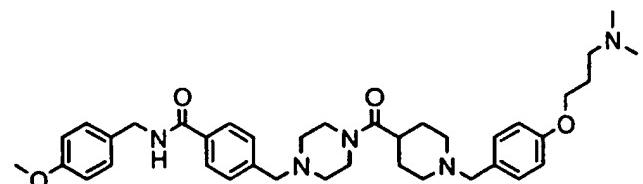
- 73 -



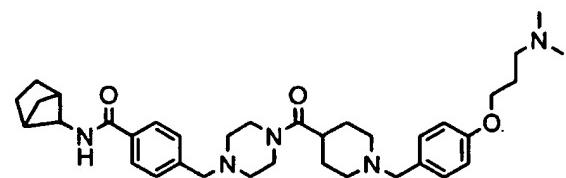
249



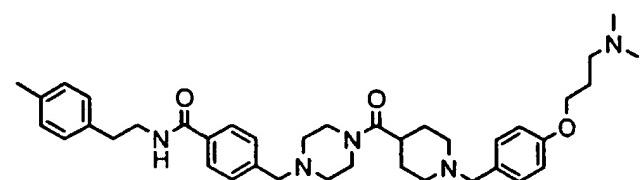
250



251

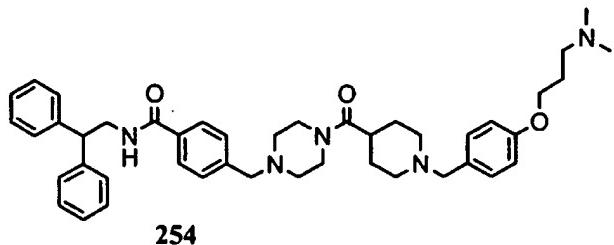


252

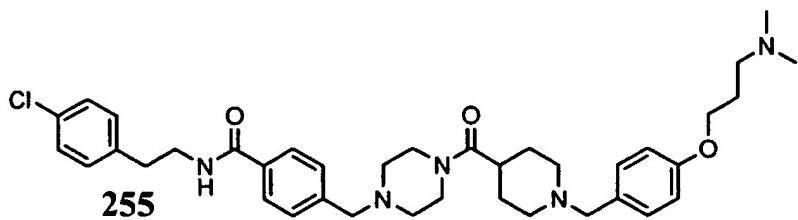


253

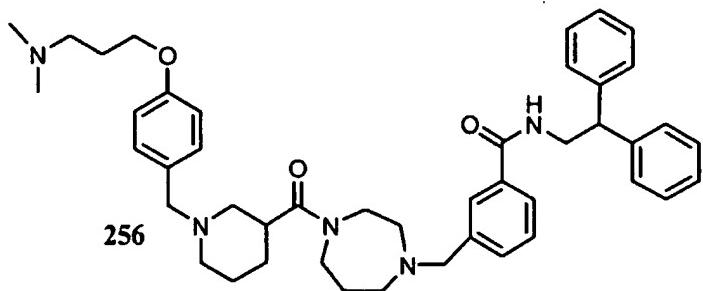
- 74 -



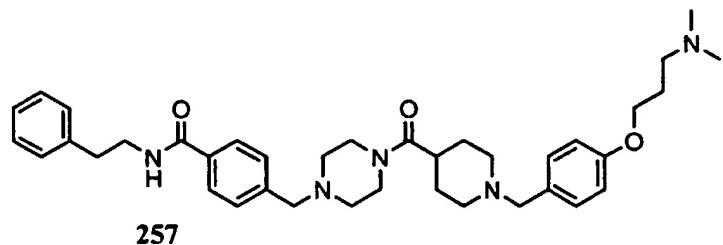
254



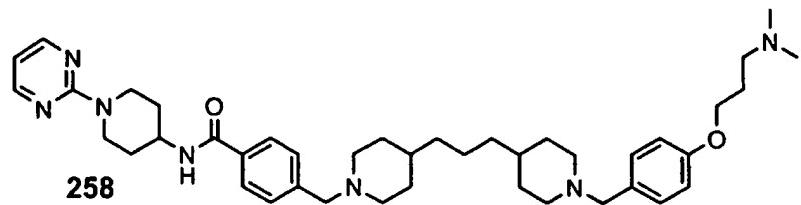
255



256

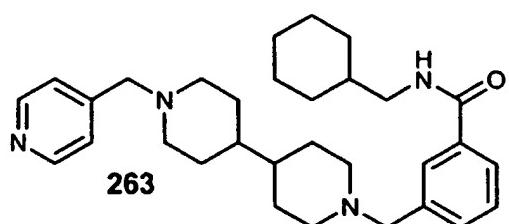
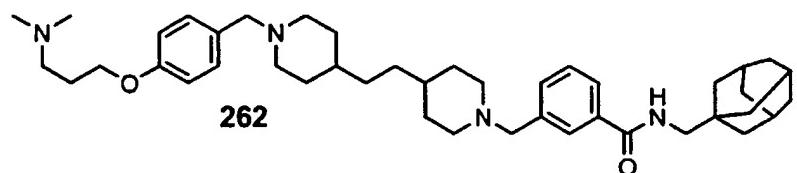
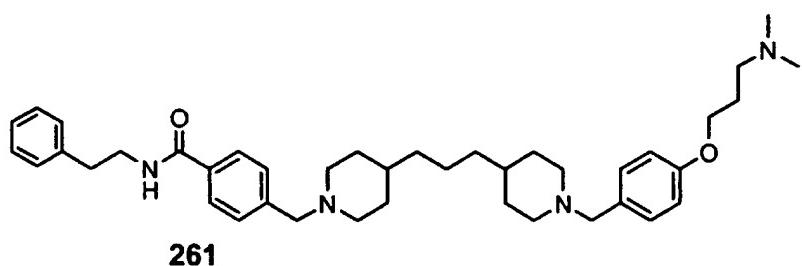
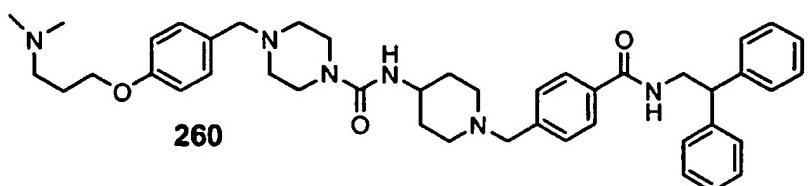
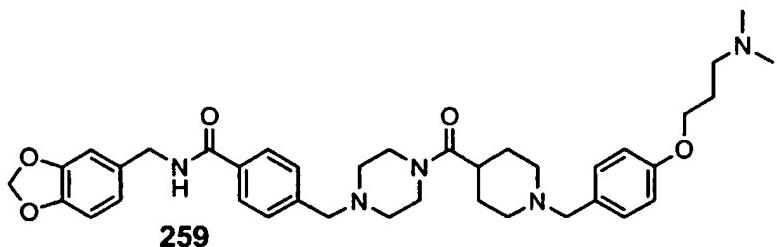


257

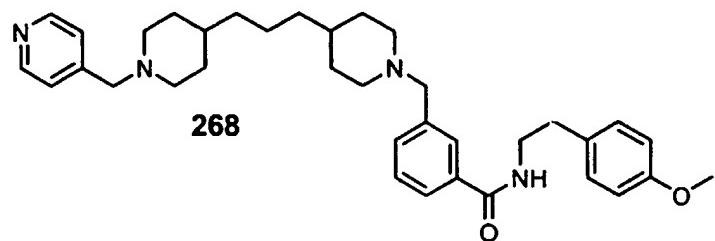
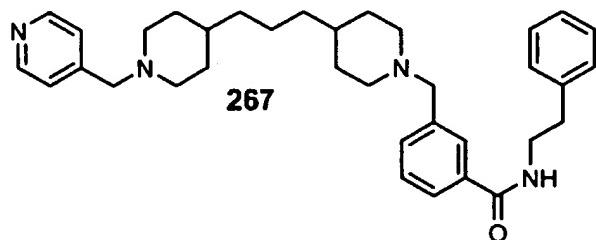
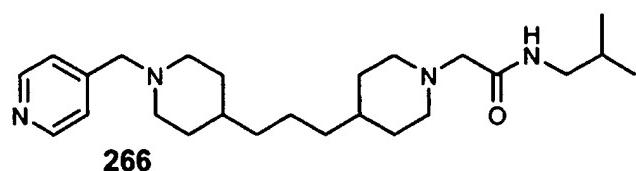
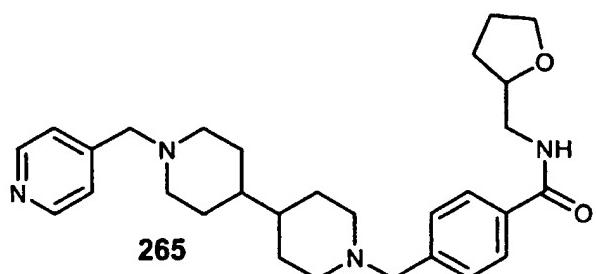
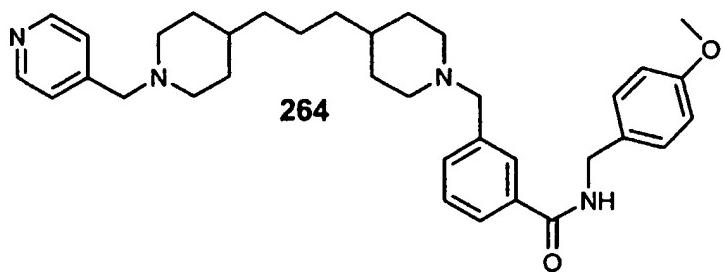


258

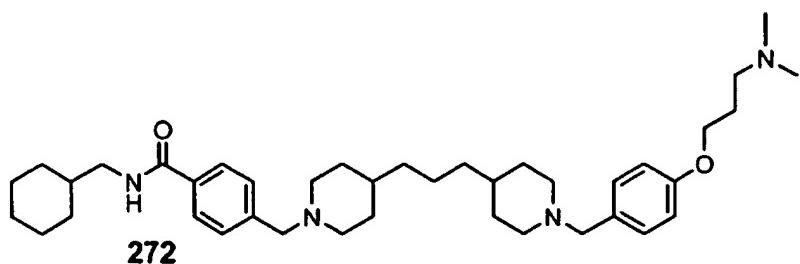
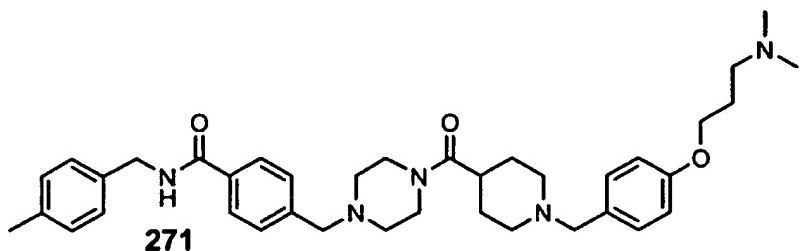
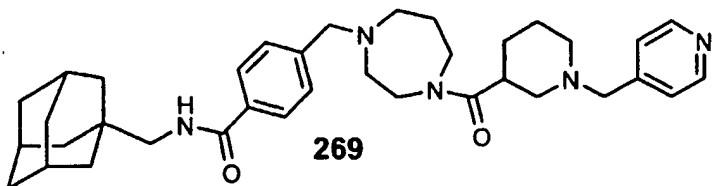
- 75 -



- 76 -

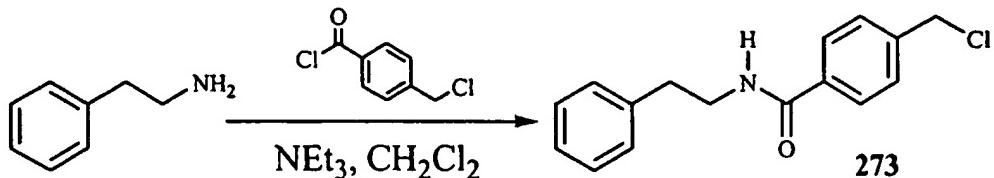


- 77 -



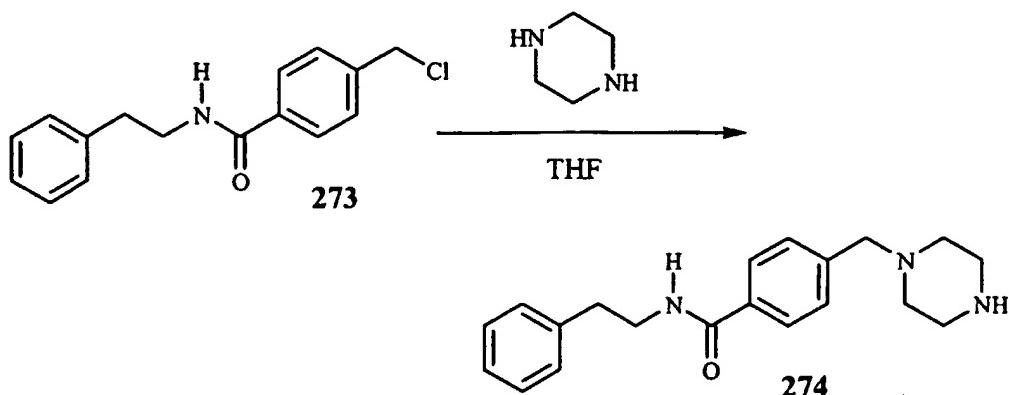
EXAMPLE 19

Compound **218** was prepared in solution in large quantity. The following is the procedure for the preparation of **218**, which serves as the general protocol for preparation of other analogs.

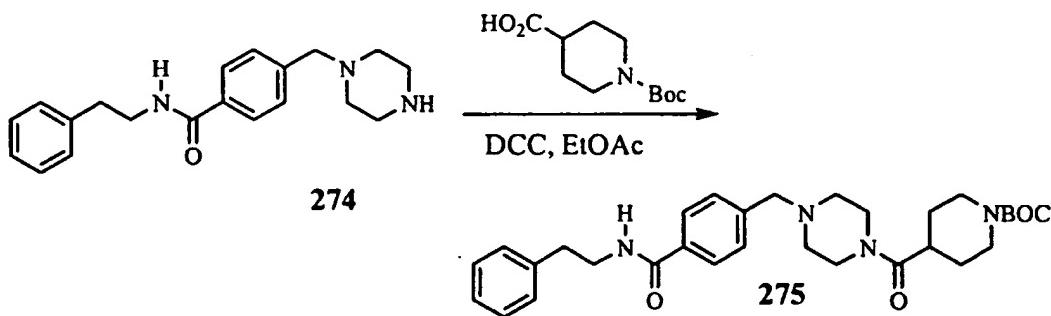


To a solution of Phenylethyl amine (120 mg, 1 mmole) and triethyl amine (200 mg, 2 mmole) in CH_2Cl_2 (10 mL) at 0 °C was added 4-(Chloromethyl)benzoyl chloride (230 mg, 1.2 mmole). After 30 min., the reaction mixture was poured into a separational funnel and washed with 1N HCl (10 mL), 1N NaOH (10 mL) and brine (10 mL). The organic layer was separated, dried over Na_2SO_4 , and filtered. The filtrate was concentrated to give compound **273** as colorless oil (260 mg, 95%).

- 78 -

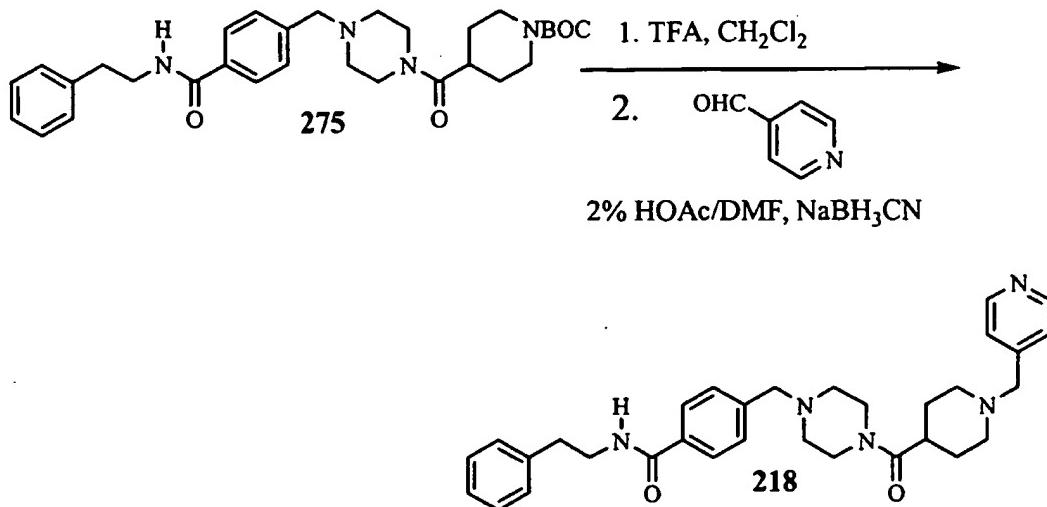


To a refluxed solution of compound **273** (260 mg, 0.95 mmole) in THF (10 mL) was added piperazine (430mg, 5 mmole). The mixture was under reflux for 1h and cooled to room temperature. Solvent was removed and the residue was dissolved in EtOAc (20 mL), which was washed with H₂O (2 x 10 mL), 1N NaOH (10 mL) and brine (10 mL). The organic layer was separated, dried over Na₂SO₄, and filtered. The filtrate was concentrated to give compound **274** as a slightly yellow oil (290 mg, 95%).



To a solution of Boc-isonipecotic acid (230 mg, 1 mmole) in EtOAc (10 mL) at 0°C was added DCC (206 mg, 1 mmole) followed by the addition of compound **274** (290 mg, 0.9 mmole) in EtOAc (5 mL). The reaction mixture was stirred at room temperature for 8h, and filtered. The filtrate was concentrated. Flash chromatography of the residue gave compound **275** as a colorless oil (390 mg, 80%)

- 79 -



To a solution of compound **275** (270 mg, 0.5 mmole) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (0.5 mL). After 30 min., the mixture was concentrated, and the residue was dissolved in EtOAc (10 mL), which was washed with 1N NaOH (10 mL) and brine (10 mL). The organic layer was separated, dried over Na_2SO_4 and filtered. The filtrate was concentrated and the residue was dissolved in DMF (5 mL). Acetic acid (0.2 mL), 4-pyridinecarboxaldehyde (64 mg, 0.6 mmole) and NaBH_3CN (64 mg, 1 mmole) were added to the solution. The reaction mixture was kept at room temperature for 8h. EtOAc (15 mL) and H_2O (10 mL) were added to the mixture, and the mixtures were poured into a separational funnel. The organic layer was washed with H_2O (10 mL), 1N NaOH (10 mL) and brine (10 mL), separated and dried over Na_2SO_4 . After filtration, the filtrate was concentrated. Flash chromatography of the residue to give compound **218** as a white foam (132 mg, 50%).

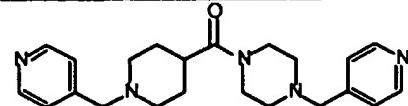
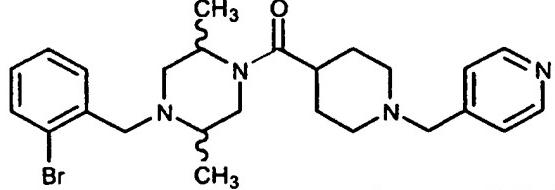
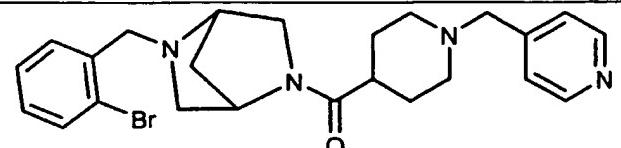
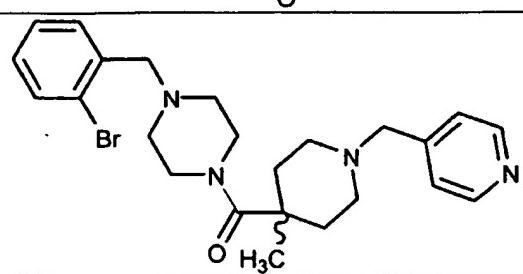
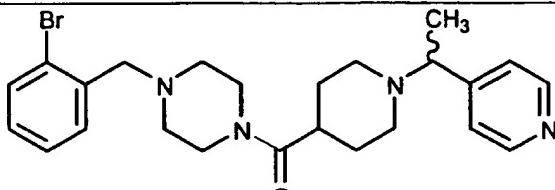
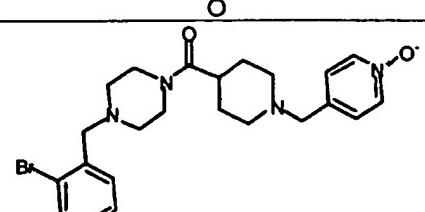
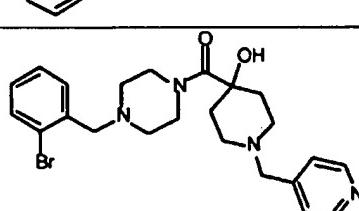
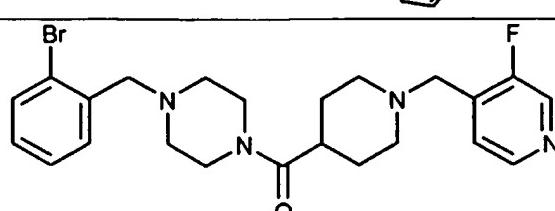
Following the procedure of Examples 1 to 17 the compounds in Table 5 were prepared.

- 80 -

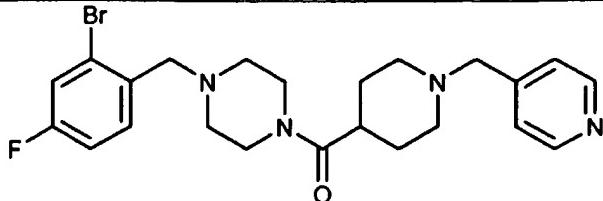
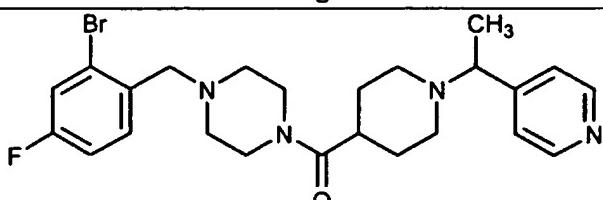
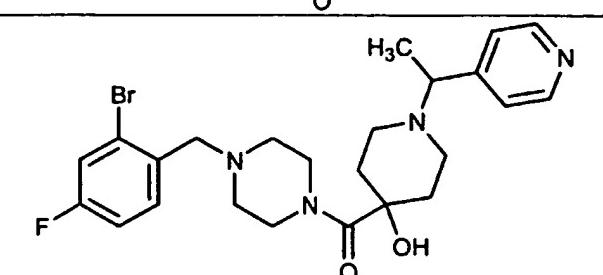
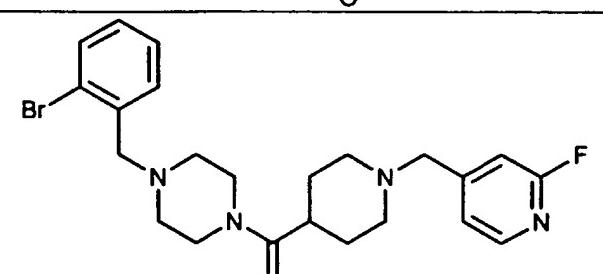
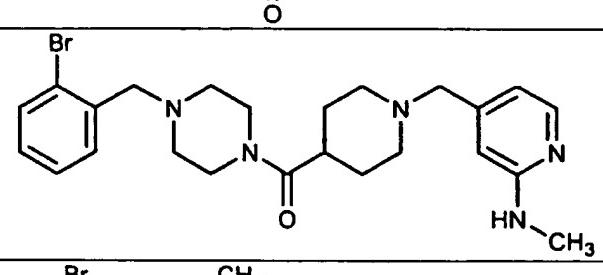
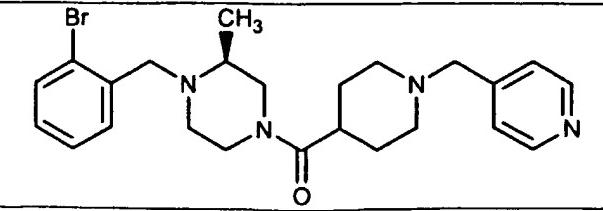
TABLE 5

Compound No.	Structure
276	
277	
278	
279	
280	
281	
282	
284	

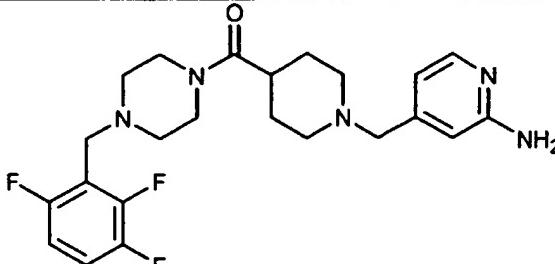
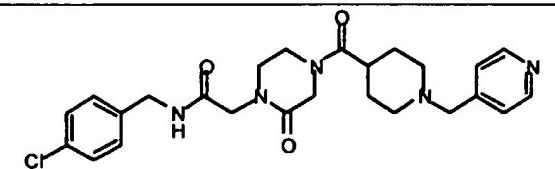
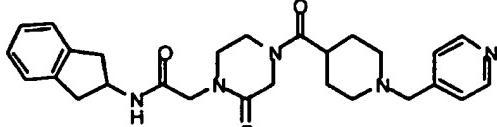
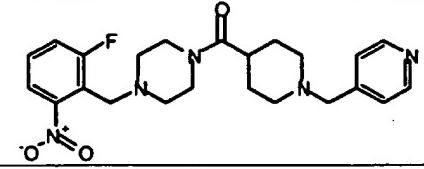
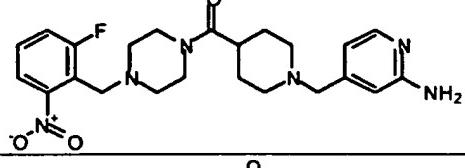
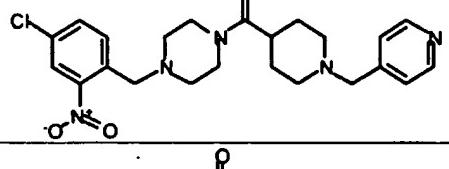
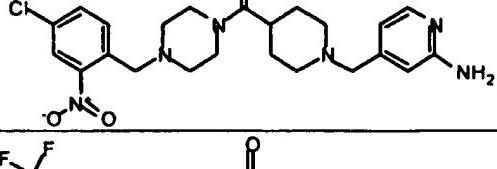
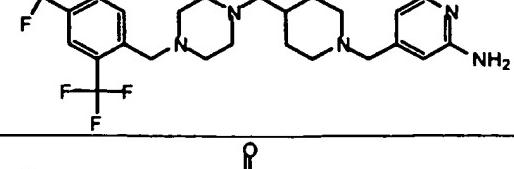
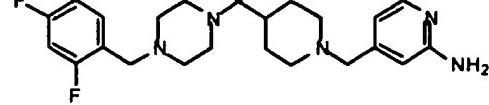
- 81 -

285	
287	
288	
289	
290	
291	
292	
293	

- 82 -

294	
295	
296	
297	
298	
299	
300	

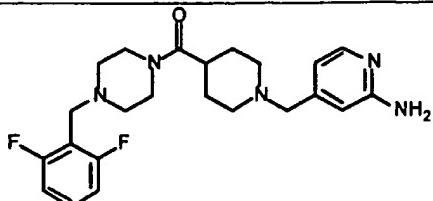
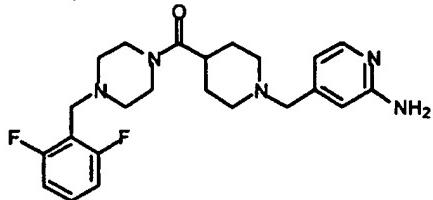
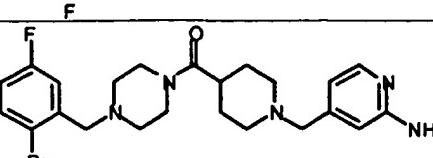
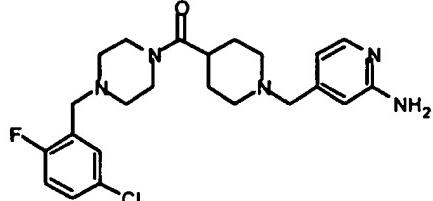
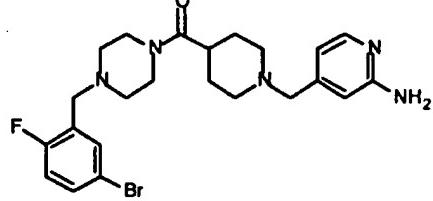
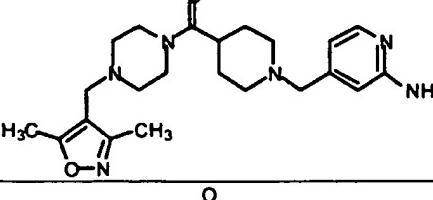
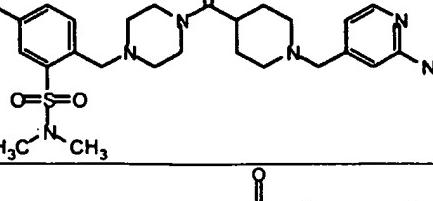
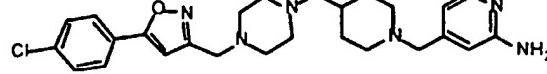
- 83 -

306	
309	
310	
311	
312	
313	
314	
315	
316	

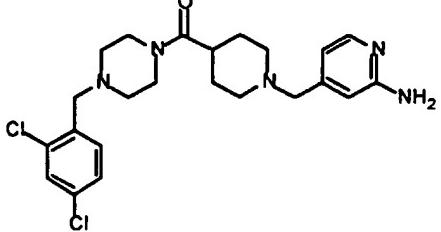
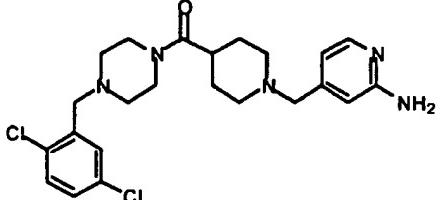
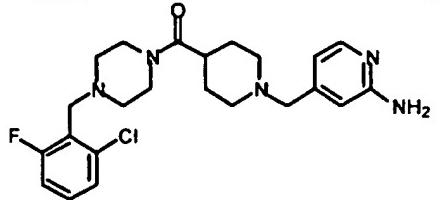
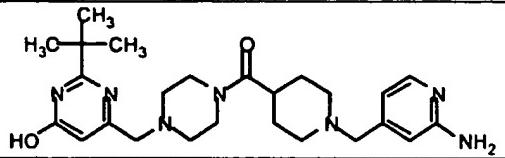
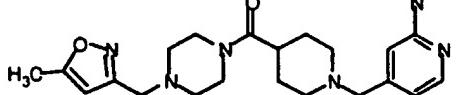
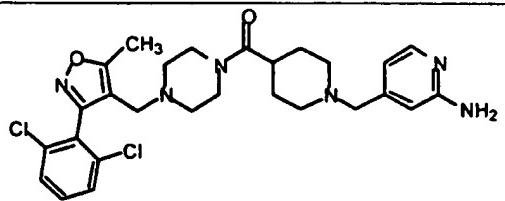
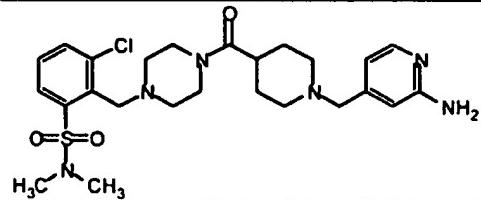
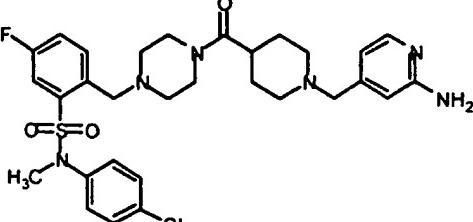
- 84 -

317	
318	
319	
321	
322	
323	
324	
325	

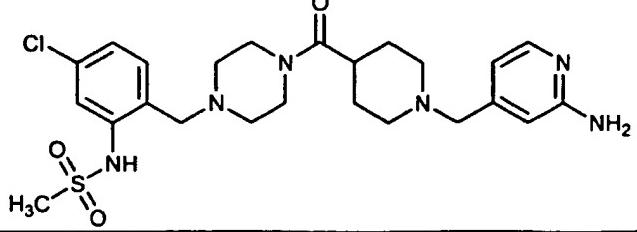
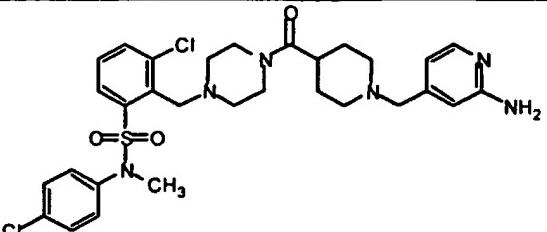
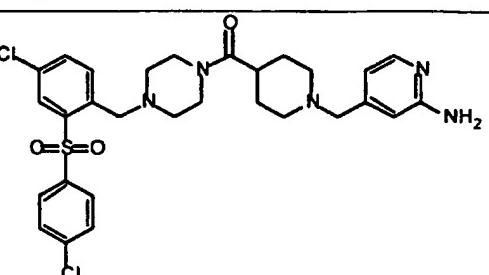
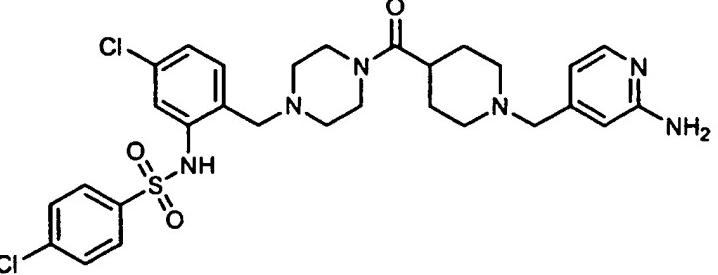
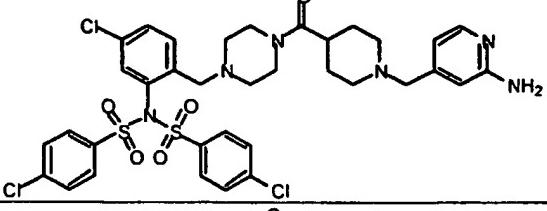
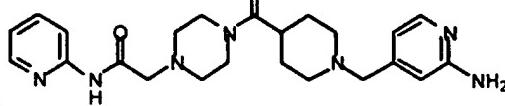
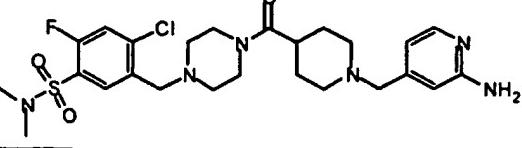
- 85 -

326	
327	
328	
329	
330	
331	
332	
333	

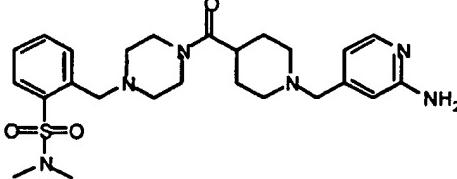
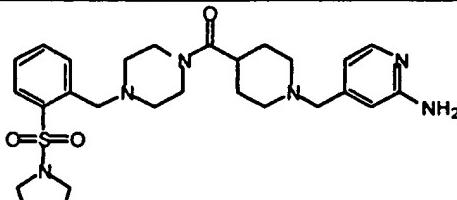
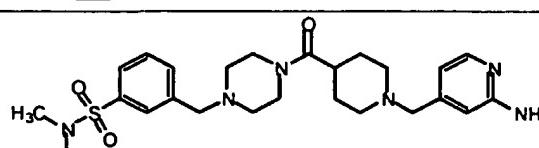
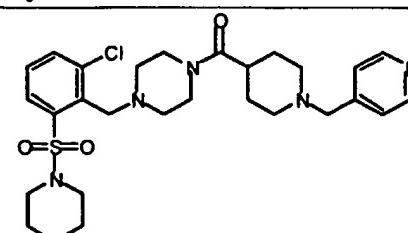
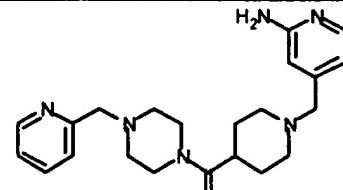
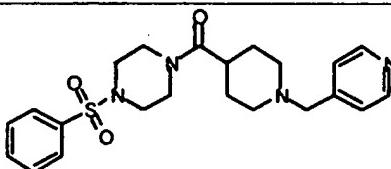
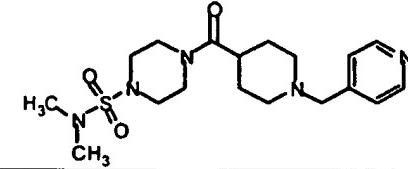
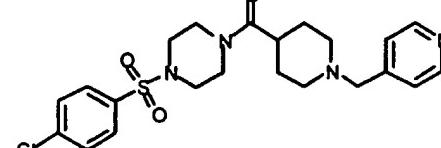
- 86 -

334	
335	
336	
338	
339	
340	
342	
343	

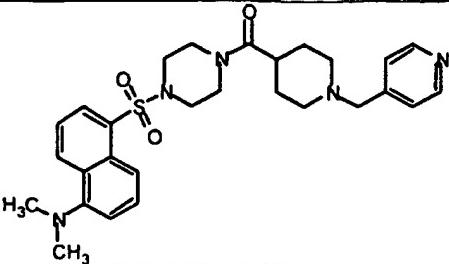
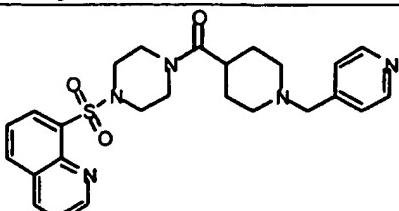
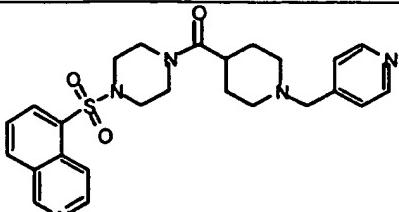
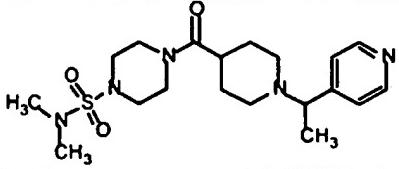
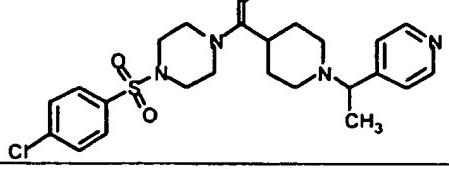
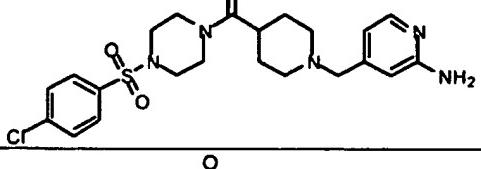
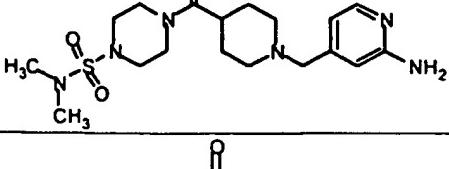
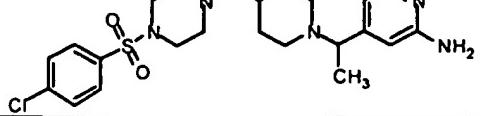
- 87 -

344	
345	
346	
347	
348	
349	
351	

- 88 -

352	
353	
354	
355	
356	
357	
358	
359	

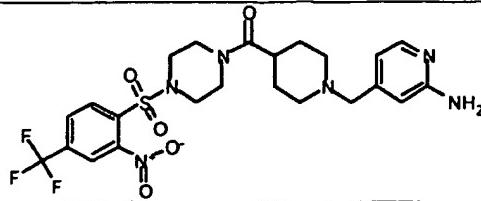
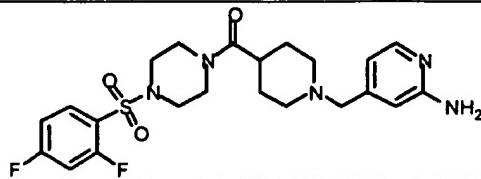
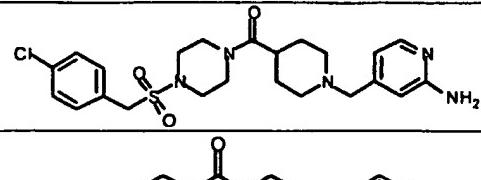
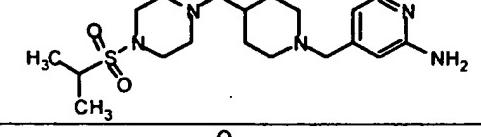
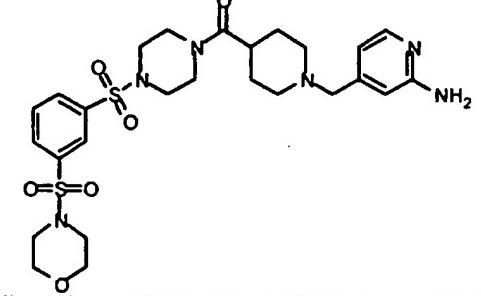
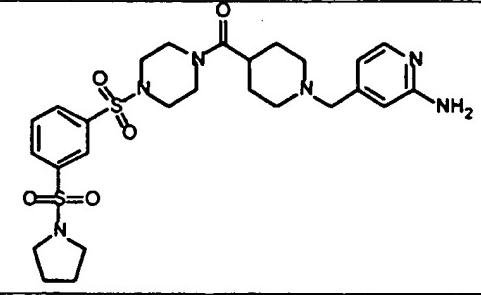
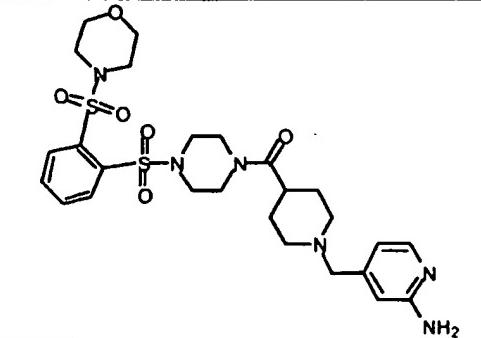
- 89 -

360	
361	
363	
364	
365	
366	
367	
368	

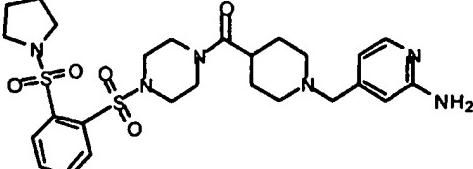
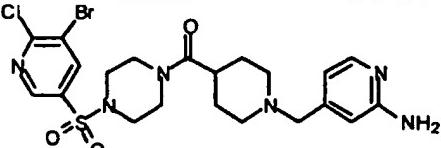
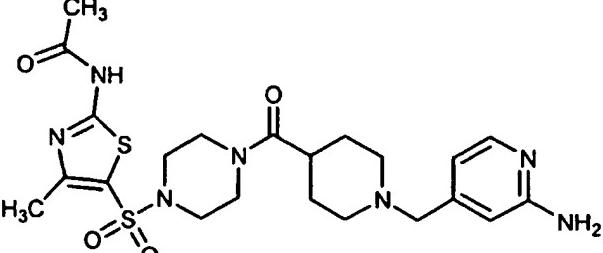
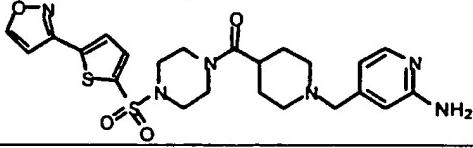
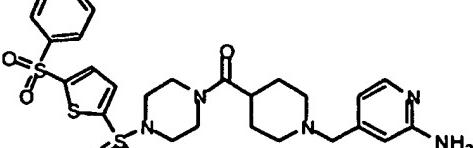
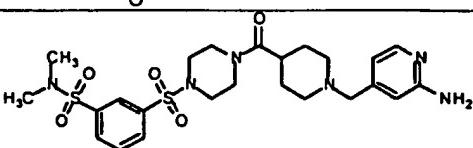
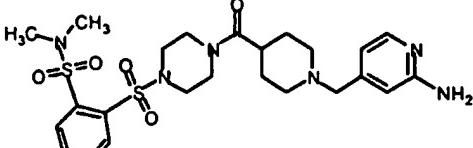
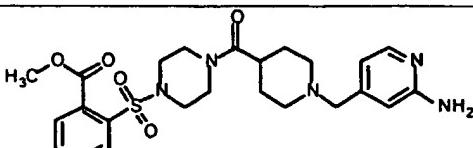
- 90 -

369	
370	
371	
374	
375	
376	
377	
380	

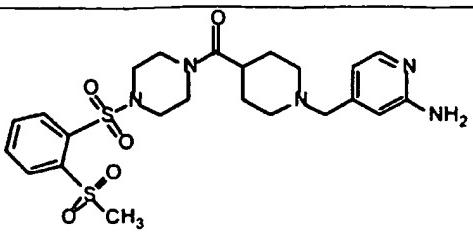
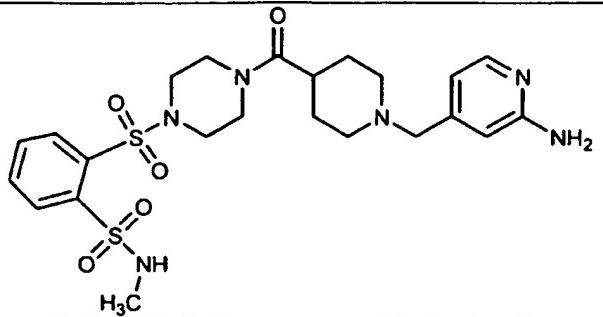
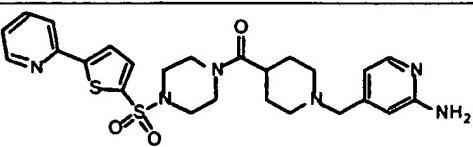
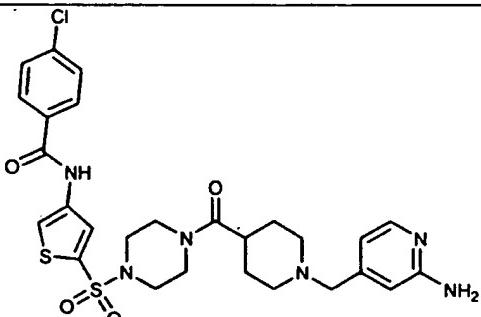
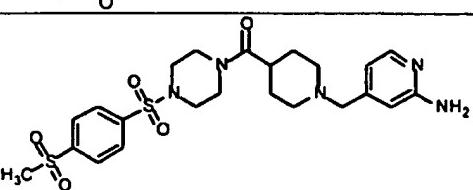
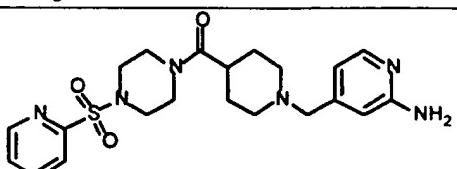
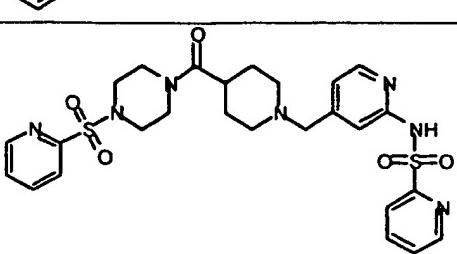
- 91 -

381	
382	
383	
387	
388	
389	
390	

- 92 -

392	
393	
394	
395	
396	
397	
398	
399	

- 93 -

400	
401	
402	
403	
404	
405	
406	

- 94 -

408	
409	
410	

General Procedure for H₃-Receptor Binding Assay

The source of the H₃ receptors in this experiment was guinea pig brain. The animals weighed 400-600 g. The brain tissue was homogenized with a solution of 50 mM Tris, pH 7.5. The final concentration of tissue in the homogenization buffer was 10% w/v. The homogenates were centrifuged at 1,000 x g for 10 min. in order to remove clumps of tissue and debris. The resulting supernatants were then centrifuged at 50,000 x g for 20 min. in order to sediment the membranes, which were next washed three times in homogenization buffer (50,000 x g for 20 min. each). The membranes were frozen and stored at -70°C until needed.

All compounds to be tested were dissolved in DMSO and then diluted into the binding buffer (50 mM Tris, pH 7.5) such that the final concentration was 2 µg/ml with 0.1% DMSO. Membranes were then added (400 µg of protein) to the reaction tubes. The reaction was started by the addition of 3 nM [³H]R- α -methyl histamine (8.8 Ci/mmol) or 3 nM [³H]N α -methyl histamine (80 Ci/mmol) and continued under incubation at 30°C for 30 min. Bound ligand was separated from unbound ligand by filtration, and the amount of radioactive ligand bound to the membranes was quantitated by liquid scintillation spectrometry. All incubations were performed in duplicate and the standard error was always less than 10%. Compounds that

- 95 -

inhibited more than 70% of the specific binding of radioactive ligand to the receptor were serially diluted to determine a K_i (nM).

Compounds 89 to 157, 159 to 168, 276 to 279, 282, 284, 285, 287 to 300, 306, 309 to 319, 321 to 336, 338 to 340, 342 to 349, 351 to 361, 363 to 371, 374 to 377, 380 to 383, 387 to 390, 392 to 406, and 408 to 410 had a K_i within the range of about 0.2 to about 600 nM.

Preferred Compounds 93, 276, 306, 317, 328, 331, 332, 333, 336, 343, 366, 367, 374 and 376 had a K_i within the range of about 0.2 to about 35 nM.

More preferred Compounds 306, 332, 333, 336, 366, 374 and 376 had a K_i within the range of about 2 to about 22 nM.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, PA.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or

- 96 -

emulsions and can be included in a transdermal patch or the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 150 mg, preferably from about 1 mg to about 75 mg, more preferably from about 1 mg to about 50 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

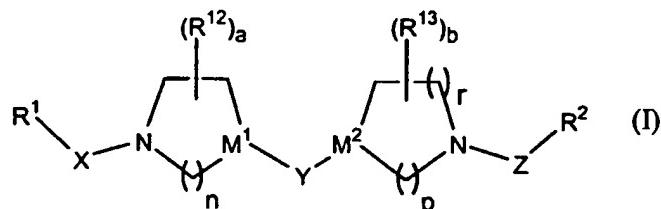
The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 300 mg/day, preferably 1 mg/day to 75 mg/day, in two to four divided doses.

While the present has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

- 97 -

WHAT IS CLAIMED IS:

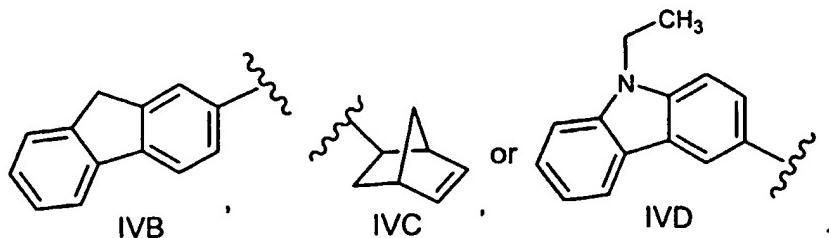
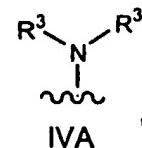
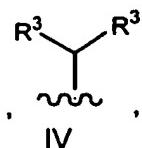
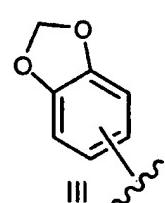
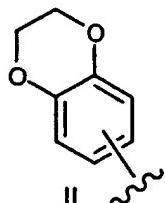
1. A compound of the formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

(A) R^1 is selected from:

- (1) aryl;
- (2) heteroaryl;
- (3) heterocycloalkyl
- (4) alkyl;
- (5) $-\text{C}(\text{O})\text{N}(\text{R}^{48})_2$;
- (6) cycloalkyl;
- (7) arylalkyl;
- (8) heteroarylheteroaryl; or
- (9) a group selected from:



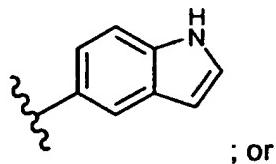
- 98 -

said aryl, heteroaryl, aryl portion of arylalkyl, phenyl ring of formula II, phenyl ring of formula III, phenyl rings of formula IVB, or phenyl rings of formula IVD are optionally substituted with 1 to 3 substituents independently selected from:

- (1) halogen;
 - (2) hydroxyl;
 - (3) lower alkoxy;
 - (4) -Oaryl;
 - (5) -SR²²;
 - (6) -CF₃;
 - (7) -OCF₃;
 - (8) -OCHF₂;
 - (9) -NR⁴R⁵;
 - (10) phenyl;
 - (11) NO₂,
 - (12) -CO₂R⁴;
 - (13) -CON(R⁴)₂ wherein each R⁴ is the same or different;
 - (14) -S(O)₂R²²;
 - (15) -S(O)₂N(R²⁰)₂ wherein each R²⁰ is the same or different;
 - (16) -N(R²⁴)S(O)₂R²²;
 - (17) -CN;
 - (18) -CH₂OH;
 - (19) -OCH₂CH₂OR²²;
 - (20) alkyl;
 - (21) substituted phenyl wherein said phenyl has 1 to 3 substituents independently selected from alkyl, halogen, -CN, -NO₂, -OCHF₂, -Oalkyl;
 - (22) -Oalkylaryl wherein said aryl group is optionally substituted with 1 to 3 independently selected halogens; or
 - (23) phenyl;
- (B) X is selected from alkyl or -S(O)₂-;
- (C) Y represents
- (1) a single bond; or
 - (2) Y is selected from -C(O)-, -C(S)-, -(CH₂)_q-, or -NR⁴C(O)-; with the provisos that:

- 99 -

- (a) when M¹ is N, then Y is not -NR⁴C(O)-; and
- (b) when Y is a bond, then M¹ and M² are both carbon;
- (D) M¹ and M² are independently selected from C or N;
- (E) Z is selected from: C₁-C₆ alkyl, -SO₂-, -C(O)- or -C(O)NR⁴-;
- (F) R² is selected from:
 - (1) a six-membered heteroaryl ring having 1 or 2 heteroatoms independently selected from N or N-O, with the remaining ring atoms being carbon;
 - (2) a five-membered heteroaryl ring having 1 to 3 heteroatoms selected from nitrogen, oxygen, or sulfur with the remaining ring atoms being carbon; or
 - (3) an alkyl group;
 - (4) an aryl group wherein said substituted phenyl is substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, -OCF₃, -CF₃, -CN, -NO₂, -NHC(O)CH₃, or -O(CH₂)_qN(R^{10A})₂;
 - (5) -N(R^{11A})₂ wherein each R^{11A} is independently selected from: H, alkyl or aryl;
 - (6) a group of the formula:



- (7) a heteroarylheteroaryl group;

said five membered heteroaryl ring ((F)(2) above) or six-membered heteroaryl ring ((F)(1) above) is optionally substituted with 1 to 3 substituents selected from:

- (a) halogen;
- (b) hydroxyl;
- (c) lower alkyl;
- (d) lower alkoxy;
- (e) -CF₃;
- (f) -NR⁴R⁵;
- (g) phenyl;
- (h) -NO₂;
- (i) -C(O)N(R⁴)₂ (wherein each R⁴ is the same or different);

- 100 -

- (j) $-\text{C}(\text{O})_2\text{R}^4$; or
- (k) phenyl substituted with 1 to 3 substituents independently selected from: halogen, $-\text{Oalkyl}$, $-\text{OCF}_3$, $-\text{CF}_3$, $-\text{CN}$, $-\text{NO}_2$ or $-\text{O}(\text{CH}_2)_q\text{N}(\text{R}^{10A})_2$;

(G) R^3 is selected from:

- (1) aryl;
- (2) heteroaryl;
- (3) heterocycloalkyl
- (4) alkyl; or
- (5) cycloalkyl;

wherein said aryl or heteroaryl R^3 groups is optionally substituted with 1 to 3 substituents independently selected from:

- (a) halogen;
- (b) hydroxyl;
- (c) lower alkoxy;
- (d) $-\text{Oaryl}$;
- (e) $-\text{SR}^{22}$;
- (f) $-\text{CF}_3$;
- (g) $-\text{OCF}_3$;
- (h) $-\text{OCHF}_2$;
- (i) $-\text{NR}^4\text{R}^5$;
- (j) phenyl;
- (k) $-\text{NO}_2$,
- (l) $-\text{CO}_2\text{R}^4$;
- (m) $-\text{CON}(\text{R}^4)_2$ wherein each R^4 is the same or different;
- (n) $-\text{S}(\text{O})_2\text{R}^{22}$;
- (o) $-\text{S}(\text{O})_2\text{N}(\text{R}^{20})_2$ wherein each R^{20} is the same or different;
- (p) $-\text{N}(\text{R}^{24})\text{S}(\text{O})_2\text{R}^{22}$;
- (q) $-\text{CN}$;
- (r) $-\text{CH}_2\text{OH}$;
- (s) $-\text{OCH}_2\text{CH}_2\text{OR}^{22}$; or
- (t) alkyl;

(H) R^4 is selected from:

- (1) hydrogen;

- 101 -

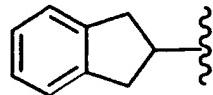
- (2) C₁-C₆ alkyl;
- (3) cycloalkyl;
- (4) cycloalkylalkyl;
- (5) heterocycloalkylalkyl;
- (6) bridged bicyclic cycloalkyl ring;
- (7) aryl having a fused heterocycloalkyl ring bound to said aryl ring;
- (8) aryl;
- (9) arylalkyl;
- (10) alkylaryl;
- (11) -(CH₂)_dCH(R^{12A})₂ wherein d is 1 to 3, and each R^{12A} is independently selected from phenyl or substituted phenyl, said substituted phenyl being substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, -OCF₃, -CF₃, -CN, or -NO₂;
- (12) heterocycloalkylheteroaryl; or
- (13) -(C₁ to C₆)alkylene-O-R²²;

wherein the aryl R⁴ group, the aryl portion of the arylalkyl R⁴ group, or the aryl portion of the alkylaryl R⁴ group is optionally substituted with 1 to 3 substituents independently selected from:

- (a) halogen;
- (b) hydroxyl;
- (c) lower alkyl;
- (d) lower alkoxy;
- (e) -CF₃;
- (f) -N(R²⁰)(R²⁴),
- (g) phenyl;
- (h) -NO₂;
- (i) -C(O)N(R²⁰)₂ (wherein each R²⁰ is the same or different),
- (j) -C(O)R²²,
- (l) -(CH₂)_k-cycloalkyl;
- (m) -(CH₂)_q-aryl; or
- (n) -(CH₂)_m-OR²²;

- 102 -

- (I) each R^{4B} is independently selected from: H, heteroaryl, alkyl, alkenyl, a group of the formula



arylalkyl, or arylalkyl wherein the aryl moiety is substituted with 1-3 substituents independently selected from: halogen;

- (J) R^5 is selected from: hydrogen, C₁-C₆ alkyl, -C(O) R^{20} , -C(O)₂ R^{20} , -C(O)N(R^{20})₂ (wherein each R^{20} is the same or different);

- (K) each R^{10A} is independently selected from H or C₁ to C₆ alkyl, or each R^{10A} , taken together with the nitrogen atom to which they are bound, forms a 4 to 7 membered heterocycloalkyl ring;

- (L) R^{12} is

- (1) selected from alkyl, hydroxyl, alkoxy, or fluoro, provided that when R^{12} is hydroxy or fluoro then R^{12} is not bound to a carbon adjacent to a nitrogen; or
- (2) R^{12} forms an alkyl bridge from one ring carbon to another ring carbon;

- (M) R^{13} is

- (1) selected from alkyl, hydroxyl, alkoxy, or fluoro, provided that when R^{13} is hydroxy or fluoro then R^{13} is not bound to a carbon adjacent to a nitrogen; or
- (2) R^{13} forms an alkyl bridge from one ring carbon to another ring carbon;

- (N) R^{20} is selected from hydrogen, alkyl, or aryl, wherein said aryl group is optionally substituted with from 1 to 3 groups independently selected from: halogen, -CF₃, -OCF₃, hydroxyl, or methoxy; or when two R^{20} groups are present, said two R^{20} groups taken together with the nitrogen to which they are bound form a five or six membered heterocyclic ring;

- (O) R^{22} is selected from: heterocycloalkyl, alkyl or aryl, wherein said aryl group is optionally substituted with 1 to 3 groups independently selected from halogen, -CF₃, -OCF₃, hydroxyl, or methoxy;

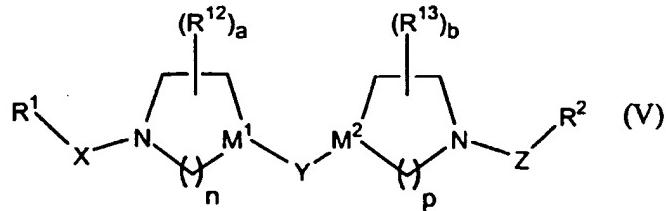
- 103 -

(P) R^{24} is selected from: hydrogen, alkyl, $-SO_2R^{22}$, or aryl, wherein said aryl group is optionally substituted with 1 to 3 groups independently selected from halogen, $-CF_3$, $-OCF_3$, hydroxyl, or methoxy;

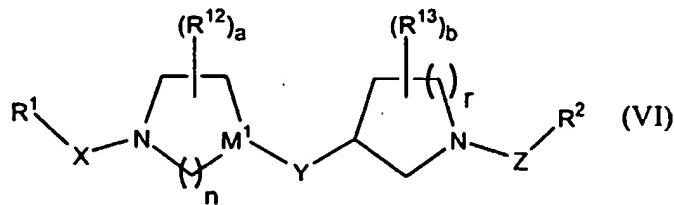
- (Q) a is 0 to 2;
- (R) b is 0 to 2;
- (S) k is 1 to 5;
- (T) m is 2 to 5;
- (U) n is 1, 2 or 3 with the proviso that when M^1 is N, then n is not 1;
- (V) p is 1, 2 or 3 with the proviso that when M^2 is N, then p is not 1;
- (W) q is 1 to 5; and
- (X) r is 1, 2, or 3 with the proviso that when r is 2 or 3, then M^2 is C and p is

1.

2. The compound of Claim 1 having the formula:



3. The compound of Claim 1 having the formula:



4. The compound of Claim 1 wherein R^1 is selected from:

- (1) substituted aryl;
- (2) substituted heteroaryl; or
- (3) formula IVA wherein each R^3 is independently selected.

5. The compound of Claim 4 wherein R^1 is selected from:

- (1) substituted phenyl;

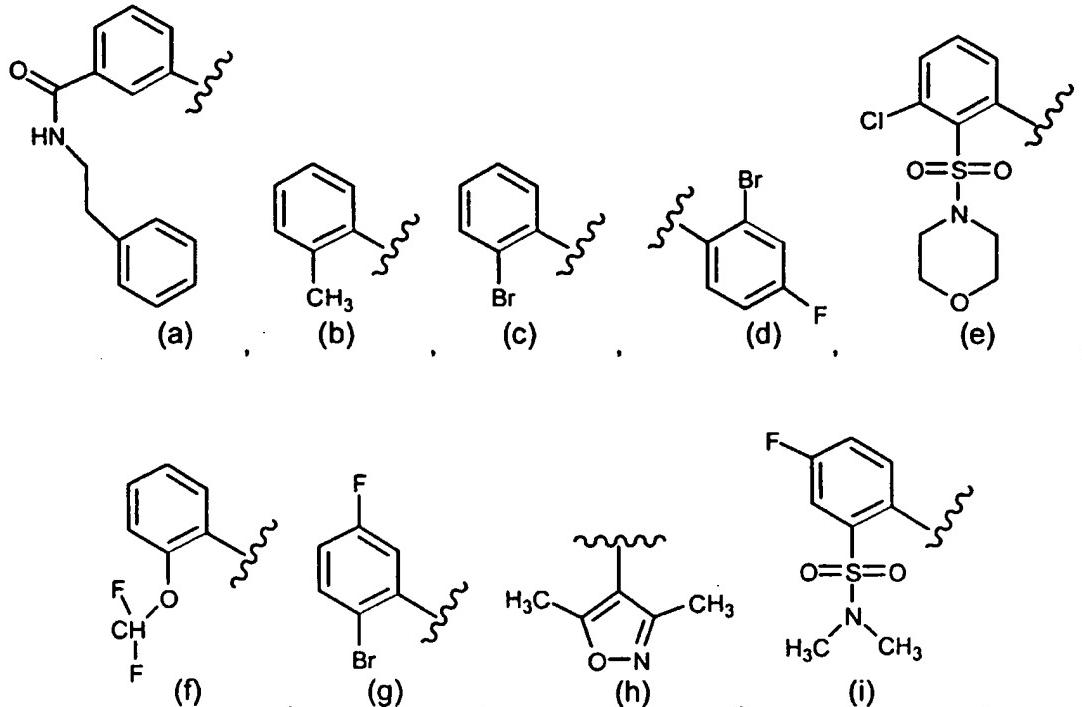
- 104 -

- (2) substituted isoxazolyl; or
- (3) -N(CH₃)₂.

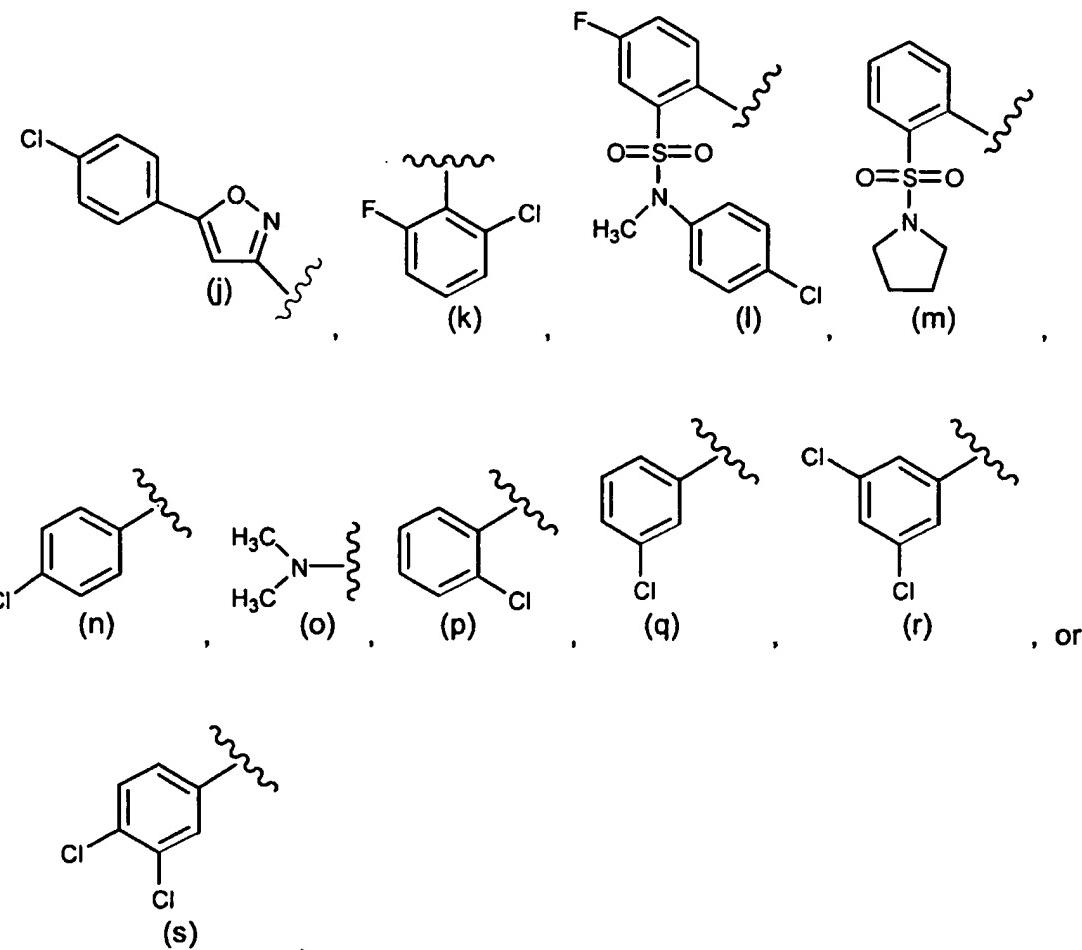
6. The compound of Claim 5 wherein R¹ is selected from:

- (1) substituted phenyl wherein said phenyl group has 1 to 3 groups selected independently selected from:
 - (a) -C(O)N(R⁴)₂;
 - (b) halo;
 - (c) -S(O)₂R²²;
 - (d) -OCF₃;
 - (e) -OCHF₂; or
 - (f) -S(O)₂N(R²⁰)₂; or
- (2) substituted isoxazolyl wherein said isoxazolyl group has 1 or 2 substituents independently selected from:
 - (a) alkyl; or
 - (b) substituted phenyl.

7. The compound of Claim 1 wherein R¹ is selected from:



- 105 -



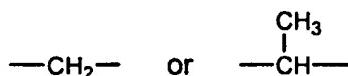
8. The compound of Claim 1 wherein X is $-\text{CH}_2-$ or $-\text{SO}_2^-$.
9. The compound of Claim 1 wherein M¹ is nitrogen.
10. The compound of Claim 9 wherein n is 2.
11. The compound of Claim 1 wherein Y is $-\text{C}(\text{O})-$.
12. The compound of Claim 1 wherein M² is C.
13. The compound of Claim 12 wherein p is 2.

- 106 -

14. The compound of Claim 1 wherein r is 1.

15. The compound of Claim 1 wherein Z is an alkyl group.

16. The compound of Claim 15 wherein Z is

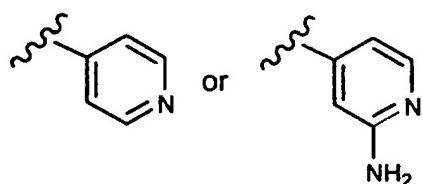


17. The compound of Claim 1 wherein R² is a six membered heteroaryl ring or a substituted six membered heteroaryl ring.

18. The compound of Claim 17 wherein R² is pyridyl or substituted pyridyl.

19. The compound of Claim 18 wherein said substituted pyridyl is substituted with -NH₂.

20. The compound of Claim 18 wherein R² is selected from:



21. The compound of Claim 1 wherein a is 0 and b is 0.

22. The compound of Claim 1 wherein:

(A) R¹ is selected from:

(1) substituted aryl;

(2) substituted heteroaryl; or

(3) formula IVA wherein each R³ is independently selected.

(B) X is -CH₂- or -SO₂-;

(C) M¹ is nitrogen;

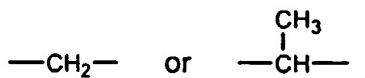
(D) n is 2;

(E) Y is -C(O)-;

- 107 -

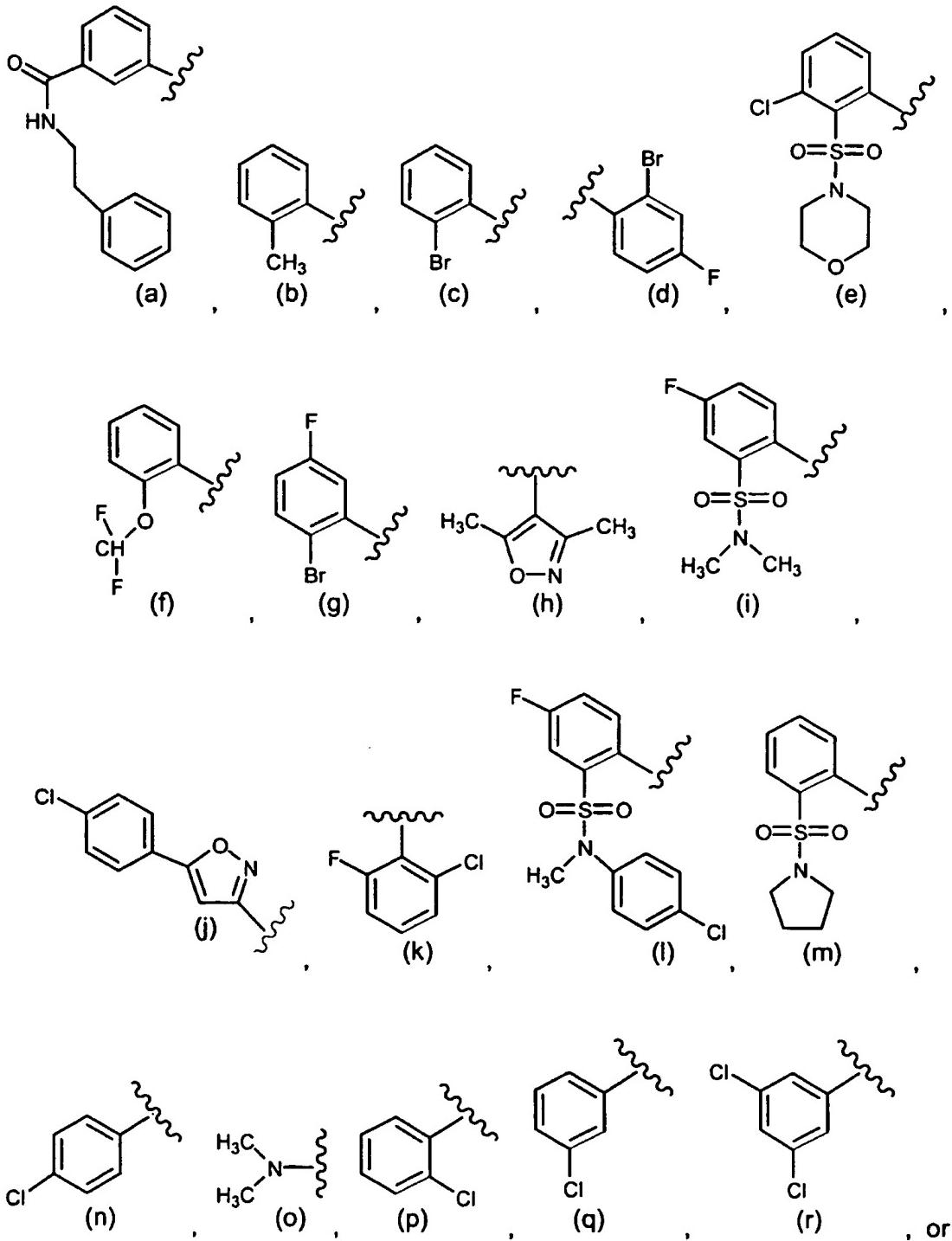
- (F) M^2 is C;
- (G) p is 2;
- (H) r is 1;
- (I) Z is an alkyl group;
- (J) R^2 is a six membered heteroaryl ring or a substituted six membered heteroaryl ring;
- (K) a is 0; and
- (L) b is 0.

23. The compound of Claim 22 wherein R^1 is selected from:
 - (1) substituted phenyl;
 - (2) substituted isoxazolyl; or
 - (3) $-N(CH_3)_2$.
24. The compound of Claim 23 wherein R^2 is pyridyl or substituted pyridyl.
25. The compound of Claim 24 wherein Z is selected from:

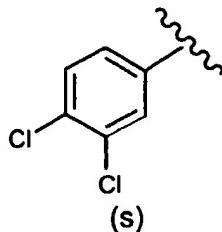


- 108 -

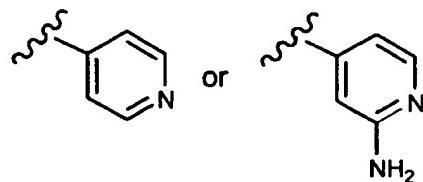
26. The compound of Claim 25 wherein R¹ is selected from:



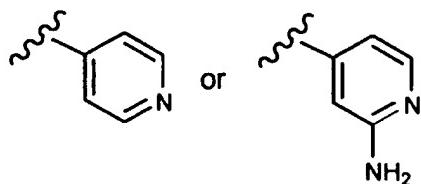
- 109 -



27. The compound of Claim 25 wherein R² is selected from:



28. The compound of Claim 26 wherein R² is selected from:



29. The compound of Claim 1 selected from: Compound 18, 25, 26, 31, 33, 37, 41, 45, 49, 51, 52, 57, 58 to 67, 73 to 84, 89 to 157, 159 to 168, 212 to 269, 271 to 272, 276 to 282, 284, 285, 287 to 300, 306, 309 to 319, 321 to 336, 338 to 340, 342 to 349, 351 to 361, 363 to 371, 374 to 377, 380 to 383, 387 to 390, 392 to 406, and 408 to 410.

30. The compound of Claim 1 selected from: 93, 276, 306, 317, 331, 332, 333, 336, 366, 343, 366, 367, 374, or 376.

31. The compound of Claim 1 selected from: Compounds 306, 332, 333, 336, 366, 374, or 376.

32. A pharmaceutical composition comprising an effective amount of a compound of Claim 1 and a pharmaceutically effective carrier.

- 110 -

33. A method of treating: allergy, allergy-induced airway responses, congestion, hypotension, cardiovascular disease, hypotension, diseases of the GI tract, hyper and hypo motility and acidic secretion of the gastro-intestinal tract, obesity, sleeping disorders, disturbances of the central nervous system, attention deficit hyperactivity disorder, hypo and hyperactivity of the central nervous system, Alzheimer's disease, schizophrenia, and migraine comprising administering to a patient in need of such treatment an effective amount of a compound of Claim 1.

34. The method of Claim 33 wherein allergy-induced airway responses are treated.

35. The method of Claim 33 wherein allergy or nasal congestion is treated.

36. A pharmaceutical composition comprising an effective amount of a compound of Claim 1, and an effective amount of H₁ receptor antagonist, and a pharmaceutically effective carrier.

37. A method of treating: allergy, allergy-induced airway responses, and congestion comprising administering to a patient in need of such treatment an effective amount of a compound of Claim 1 in combination with an effective amount of an H₁ receptor antagonist.

38. The method of Claim 37 wherein said H₁ receptor antagonist is selected from: astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carboxamine, descarboethoxyloratadine, diphenhydramine, doxylamine, dimethindene, ebastine, epinastine, fletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, meclizine, mizolastine, mequitazine, mianserin, noberastine, norastemizole, picumast, pyrilamine, promethazine, terfenadine, tripeleannamine, temelastine, trimeprazine or triprolidine.

39. The method of Claim 38 wherein said H₁ receptor antagonist is selected from: loratadine, descarboethoxyloratadine, fexofenadine or cetirizine.

- 111 -

40. The method of Claim 39 wherein said H₁ receptor antagonist is selected from: loratadine or descarboethoxyloratadine.

41. Use of a compound of Claim 1 for the manufacture of a medicament for treating allergy, allergy-induced airway responses, congestion, hypotension, cardiovascular disease, hypotension, disease of the GI tract, hyper and hypo motility and acidic secretion of the gastro-intestinal tract, obesity, sleeping disorders, disturbances of the central nervous system, attention deficit hyperactivity disorder, hypo and hyperactivity of the central nervous system, Alzheimer's disease, schizophrenia, and migraine.

42. Use of a compound of Claim 1 and use of an H₁ receptor antagonist for the manufacture of a medicament for treating allergy, allergy-induced airway responses, congestion, hypotension, cardiovascular disease, hypotension, disease of the GI tract, hyper and hypo motility and acidic secretion of the gastro-intestinal tract, obesity, sleeping disorders, disturbances of the central nervous system, attention deficit hyperactivity disorder, hypo and hyperactivity of the central nervous system, Alzheimer's disease, schizophrenia, and migraine.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 September 2002 (19.09.2002)

PCT

(10) International Publication Number
WO 02/072570 A3

(51) International Patent Classification⁷: **C07D 401/14, 401/12, 413/14, 417/14, 498/04, A61K 31/4545, 31/495, A61P 37/08**

(74) Agent: JEANETTE, Henry, C.; Schering-Plough Corporation, Patent Department - K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(21) International Application Number: PCT/US02/07106

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VN, YU, ZA, ZM.

(22) International Filing Date: 11 March 2002 (11.03.2002)

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(25) Filing Language: English

(26) Publication Language: English

Declaration under Rule 4.17:

- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:

- *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
6 March 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 02/072570 A3

(54) Title: NON-IMIDAZOLE COMPOUNDS AS HISTAMINE H3 ANTAGONISTS

(57) Abstract: Disclosed are novel compounds of the formula (I). Also disclosed are pharmaceutical compositions comprising the compounds of Formula (I). Also disclosed are methods of treating various diseases or conditions, such as, for example, allergy, allergy-induced airway responses, and congestion (e.g., nasal congestion) using the compounds of Formula (I). Also disclosed are methods of treating various diseases or conditions, such as, for example, allergy, allergy-induced airway responses, and congestion (e.g., nasal congestion) using the compounds of Formula (I) in combination with a H1 receptor antagonist.

INTERNATIONAL SEARCH REPORT

1AI Application No

S 02/07106

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/14 C07D401/12 C07D413/14 C07D417/14 C07D498/04
A61K31/4545 A61K31/495 A61P37/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 02 32893 A (SCHERING CORP) 25 April 2002 (2002-04-25) * see claims 1-40 * the whole document	1-42
E	WO 02 072093 A (SCHERING CORP) 19 September 2002 (2002-09-19) * see claims * the whole document	1-42
X	US 5 889 006 A (BROWNE MARGARET E ET AL) 30 March 1999 (1999-03-30) * overlap of chemical formula, see the claims * the whole document	1-42

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the Invention
- *X* document of particular relevance; the claimed Invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- &* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the International search report

19 December 2002

03/01/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Stellmach, J

INTERNATIONAL SEARCH REPORT

AI Application No

1,00 02/07106

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 00488 A (MCCOMBIE STUART W ; SCHERING CORP (US); TAGAT JAYARAM R (US); VICE) 6 January 2000 (2000-01-06) * overlap of chemical formula, see the claims * the whole document ----	1-42
X	WO 98 05292 A (SCHERING CORP) 12 February 1998 (1998-02-12) * overlap of chemical formula, see the claims * the whole document ----	1-42
Y	WO 99 42446 A (ISHIWATA HIROYUKI ; HATTORI YUKIO (JP); KOWA CO (JP); NAKAO HIROSHI) 26 August 1999 (1999-08-26) * see claims * the whole document & EP 1 057 815 A (KOWA CO. LTD.) 6 December 2000 (2000-12-06) * see claim 1, definition of X and Y * the whole document ----	1-42
Y	STARK H ET AL: "Developments of Histamine H3-receptor Antagonists" DRUGS OF THE FUTURE, BARCELONA, ES, vol. 21, no. 5, 1996, pages 507-520, XP002084872 ISSN: 0377-8282 * see p.512, fig. 7 * the whole document ----	1-42
Y	GANELLIN, R. ET AL.: "Synthesis of Potent Non-Imidazole Histamine H3 Receptor Antagonists" ARCH.PHARM.PHARM.MED.CHEM., vol. 331, 1998, pages 395-404, XP002123596 WEINHEIM * see p.397, Table 1 * the whole document ----	1-42

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/07106

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-7 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely the structural limitation of claims 8-12 e.g those compounds recited in the examples and closely related homologous compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members				Initial Application No PCT/US 02/07106
Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0232893	A 25-04-2002	AU WO	1535502 A 0232893 A2	29-04-2002 25-04-2002
WO 02072093	A 19-09-2002	WO US	02072093 A2 2002151565 A1	19-09-2002 17-10-2002
US 5889006	A 30-03-1999	US AU AU BR CN CZ EP HU JP KR NO NZ PL SK TR WO US ZA US US US US AU AU CA EP FI HU JP NZ TW WO ZA	5883096 A 724001 B2 389997 A 9711119 A 1232462 A ,B 9900366 A3 0938483 A2 9902827 A2 2000501117 T 2000029947 A 990551 A 333801 A 331534 A1 15599 A3 9900255 T2 9805292 A2 6043255 A 9707011 A 6037352 A 6288068 B1 2002103205 A1 701452 B2 4971796 A 2212895 A1 0811002 A2 973446 A 9800792 A2 11501014 T 303415 A 464646 B 9626196 A2 9601293 A	16-03-1999 07-09-2000 25-02-1998 23-11-1999 20-10-1999 16-06-1999 01-09-1999 28-08-2000 02-02-2000 25-05-2000 07-04-1999 28-04-2000 19-07-1999 13-03-2000 21-07-1999 12-02-1998 28-03-2000 06-02-1998 14-03-2000 11-09-2001 01-08-2002 28-01-1999 11-09-1996 29-08-1996 10-12-1997 22-10-1997 30-08-1999 26-01-1999 28-10-1999 21-11-2001 29-08-1996 19-08-1996
WO 0000488	A 06-01-2000	AU CA CN EP HU JP JP TW WO ZA	4820199 A 2336000 A1 1314905 T 1091956 A1 0104058 A2 3344997 B2 2002519349 T 474933 B 0000488 A1 200007555 A	17-01-2000 06-01-2000 26-09-2001 18-04-2001 28-03-2002 18-11-2002 02-07-2002 01-02-2002 06-01-2000 15-03-2002
WO 9805292	A 12-02-1998	US AU AU BR CN CZ EP HU	5889006 A 724001 B2 389997 A 9711119 A 1232462 A ,B 9900366 A3 0938483 A2 9902827 A2	30-03-1999 07-09-2000 25-02-1998 23-11-1999 20-10-1999 16-06-1999 01-09-1999 28-08-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members			Final Application No PCT/US 02/07106	
Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
WO 9805292	A	JP 2000501117 T KR 2000029947 A NO 990551 A NZ 333801 A PL 331534 A1 SK 15599 A3 TR 9900255 T2 WO 9805292 A2 US 6043255 A ZA 9707011 A	02-02-2000 25-05-2000 07-04-1999 28-04-2000 19-07-1999 13-03-2000 21-07-1999 12-02-1998 28-03-2000 06-02-1998	
WO 9942446	A 26-08-1999	AU 747815 B2 AU 2440899 A BR 9908105 A CA 2320971 A1 CN 1291186 T EP 1057815 A1 HU 0104432 A2 WO 9942446 A1 NO 20004092 A NZ 505912 A US 6448242 B1	23-05-2002 06-09-1999 17-10-2000 26-08-1999 11-04-2001 06-12-2000 29-04-2002 26-08-1999 16-08-2000 27-09-2002 10-09-2002	